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Creatinine Excretion in Women: Data Collected in the Course of Urinalysis for Female Sex Hormones[1]

[Creatinine Excretion In Women]

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DURING THE PAST 10 YEARS this laboratory has been engaged in the quantification of female sex hormones and their excretory products in the urine of pregnant and non-pregnant women under various physiological, pathological and experimental conditions. Realizing the difficulty of procuring the full coöperation of patients and of hospital nursing staffs in obtaining accurately timed specimens, we have made it a routine to perform creatinine determinations upon all urines analyzed in order to detect gross errors in collection. This procedure is based upon Folin's accepted observation (1) that urinary creatinine is a product of endogenous metabolism and that the creatinine output for any given individual is relatively constant from day to day. With the exception of creatine determinations in the urines of 4 menstruating women, creatinine output alone has been measured, since no primary effort was being made to study creatine and creatinine metabolism in the subjects under observation. The large amount of data which has accumulated, however, contains information which may be of value in considering any possible relationship between female sex physiology and creatinine excretion. Furthermore, analysis of the data has made it possible for us to evaluate the reliability of this method of checking urine collections and the feasibility of recalculating 24-hour volumes on the basis of the creatinine content of specimens in which gross errors are apparent.

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METHODS AND RESULTS

Urinary creatine and creatinine have been measured according to the method of Folin (2). The methods utilized in the study of the excretion of female sex hormones and their excretory products have been described and most of the results reported and discussed in previous publications (3–11). The results on creatine and creatinine excretion included in this survey are exclusively from women in whom we were absolutely certain of the accuracy of collections. Twenty-four-hour volumes were obtained except where otherwise specified, and all results are expressed in terms of 24-hour excretion. No attempt was made to control the diet. No preservative was used but all specimens were kept cold during the period of collection and analyzed within 12 hours of the time of the last voiding.

Creatine and Creatinine Excretion During Menstrual Cycles

From each of 6 menstruating women, repeated urines were obtained throughout 1 to 6 complete menstrual cycles, a total of 14 cycles involving 140 creatinine determinations. In the urines of 4 of these same women, creatine was also measured during a total of 11 cycles involving 113 determinations. The cyclic variations in estrogen excretion were measured in all 6 women, from which we conclude that only 2 of the 14 cycles were anovulatory.

O. W. S. (fig. 1, table 1) was studied throughout 6 complete cycles, creatine, creatinine and total estrogen being measured in each of 60 urine specimens. The curves of estrogen excretion indicated that all 6 cycles were ovulatory with a peak in total estrogen 12 to 14 days before the next catamenia. In each, the premenstrual drop in urinary estrogen was accompanied by a rise in urinary creatinine. Menstruation itself, at which time the lowest titers for urinary estrogen pertained, was consistently associated with creatinuria and a decrease in the output of creatinine. In this individual, creatine was never demonstrable in the urine except just before and during flow. Two other individuals (a total of 3 cycles involving 27 creatinine and estrogen determinations) showed curves similar to those just described, that is, a mid-cycle peak in estrogen excretion and a drop in the 24-hour creatinine output just before or at the start of menstruation. Creatine was not measured.

L. D. Y. (fig. 2) was followed throughout 3 consecutive cycles. From the clinical history and the curves for urinary estrogen, we believe that conception and an early abortion took place during the first 38-day cycle and that this episode was followed by 2 anovulatory periods. The data on the 3d cycle are not included in the chart, since the values for all 3 constituents fall on the curves given in the second cycle. In each of the 3 cycles, 2 peaks of creatinine excretion occurred, one on the 9th to 12th days and a second 2 to 4 days before flow. As with *O. W. S.*, creatinuria consistently accompanied the onset of flow and was absent at all other times.

The other two menstruating women studied, each throughout one cycle, showed curves of estrogen excretion indicative of ovulation. In each, the creatinine curve followed the general pattern of those illustrated in figure 2 on *L. D. Y.* One of them excreted creatine throughout the cycle followed, but the amount during the luteal phase, 60 to 80 mg. in 24 hours, was consistently less than that during menstruation and follicle ripening, 180 to 340 mg. in 24 hours. The other individual excreted 30 to 200 mg. of creatine in 24 hours during the first half of a 31-day cycle, but after the 19th day, although daily specimens were analyzed, no creatine was found until the day before the onset of the next period.

The reuslts described are sufficiently consistent to suggest strongly that some correlation exists between fluctuations in creatine and creatinine excretion and ovarian activity. In all 14 cycles, a rise in creatinine excretion occurred late in the second half

TABLE 1. CREATINE AND CREATININE EXCRETION DURING 6 CYCLES IN A NORMALLY MENSTRUATING INDIVIDUAL (O.W.S.)

Day of Cycle	Cycle 1 5/5–6/3/34		Cycle 2 6/3–7/1/34		Cycle 3 7/1–29/34		Cycle 4 6/3–7/1/35		Cycle 5 7/1–29/35		Cycle 6 4/20–5/19/36	
	P.C.[1]	C.[2]	P.C.	C.	P.C.	C.	P.C.	C.	P.C.	C.	P.C.	C.
1					1.44	0.12						
2 Menstruating	1.46	0.30	1.45	0.35								
2					1.40	0.42			1.58	0.40		
4	1.45	0	1.43	0.08								
5									1.62	0		
6 or 7	1.34	0	1.34	0	1.33	0	1.46	0	1.51	0		
8 or 9							1.50	0				
10 or 11	1.32	0	1.36	0	1.35	0	1.45	0	1.54	0		
12 or 13			1.38	0	1.40	0			1.50	0		
14 or 15	1.36	0	1.46	0	1.46	0	1.45	0	1.43	0	1.37	0
16 or 17							1.52	0				
18 or 19	1.42	0	1.46	0	1.46	0	1.50	0	1.48	0	1.54	0
20 or 21	1.41	0	1.47	0					1.54	0		
22 or 23			1.50	0			1.57	0	1.57	0	1.60	0
24 or 25			1.52	0	1.58	0	1.71	0	1.69	0	1.71	0
26 or 27	1.58	0			1.43	0	1.62	0.20				
28 or 29	1.57	0	1.58	0	1.42	0			1.60	0	1.59	0.12
1 Menstruating	Continued in next column		Continued in next column		1.44	0	Continued in next column		1.55	0.22	1.42	0.20
3					1.45	0.18						
4					1.45	0						

[1] P.C. = Preformed creatinine, gm. in 24 hr.
[2] C. = Creatine as creatinine, gm. in 24 hr.

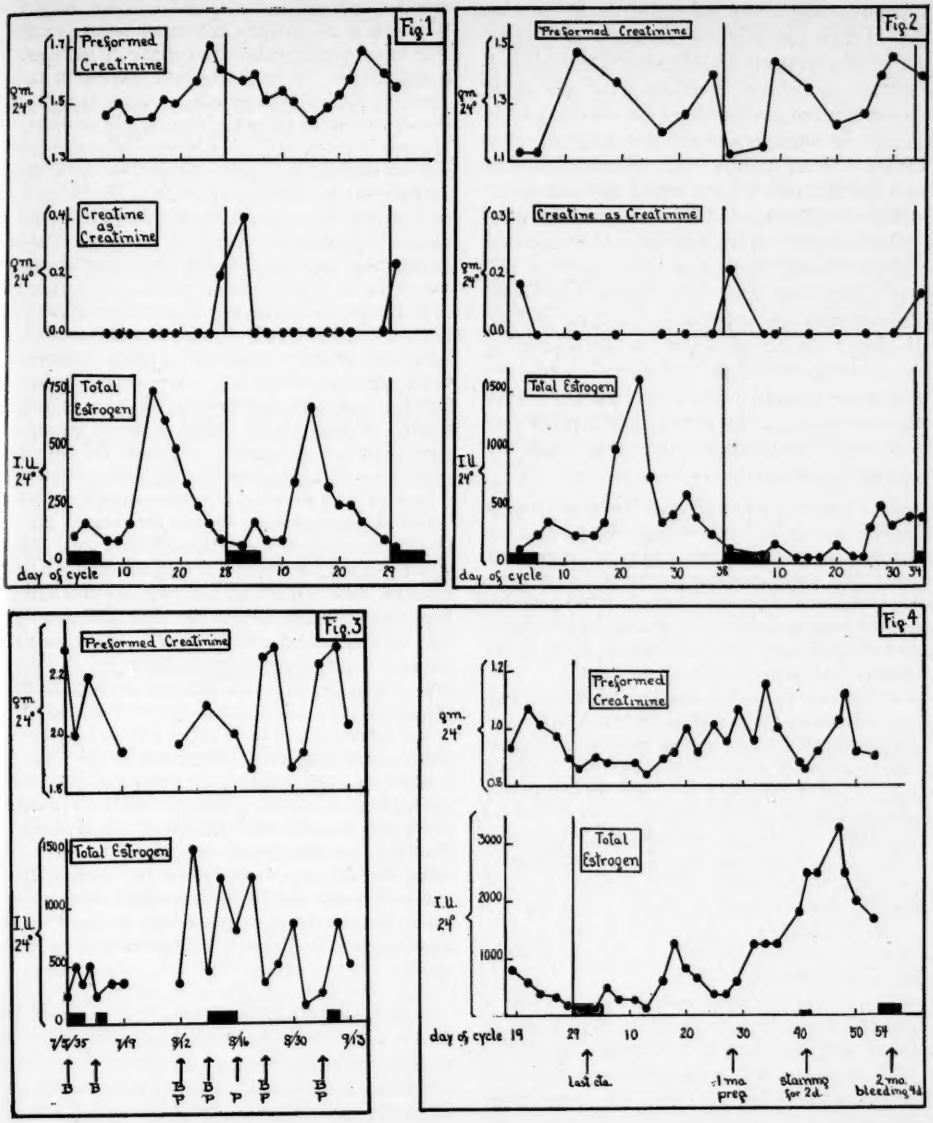

Fig. 1. CREATININE, CREATINE AND ESTROGEN EXCRETION DURING CONSECUTIVE OVULATORY CYCLES ON *O. W. S.* Fig. 2. Creatinine, creatine and estrogen excretion during consecutive cycles on *L. D. Y.* Probably an early abortion followed by an ovulatory cycle. Fig. 3. Creatinine and estrogen excretion before and during the administration of pituitary gonadotropin to a patient (*Mrs. A. G.*) with irregular catemenia, obesity and masculine hirsutism.

B = Endometrial biopsy. All specimens showed 8-day proliferation.

P = 1 cc. of Prephysin (pituitary gonadotropin) by intravenous injection. Fig. 4. Creatinine and estrogen excretion during conception and threatened abortion (*Mrs. Y. B.*). Black rectangles indicate days of flow.

and a decreased output preceded or accompanied the onset of flow. In 3 of the 6 women studied, a total of 5 cycles, a post-menstrual rise, fully as marked as that during the second half of the cycle, was observed. In 2 of the 4 women in whom urinary creatine was measured, creatinuria appeared only at the onset of flow (9 cycles). The other two (2 cycles) excreted creatine in larger amounts at this time than during the luteal phase. In one individual (*L. D. Y.*, fig. 2), the same pattern of creatine and creatinine excretion pertained

throughout 3 consecutive cycles, despite the fact that the first of these (according to the curve of estrogen excretion) was ovulatory and the other 2 anovulatory. We are led to believe, therefore, that any cyclic changes in creatine and creatinine metabolism may be considered the direct result not of ovarian secretion but rather of other changes, e.g., vascular and those of water and salt metabolism, which characterize the menstrual phenomenon, whether or not menstrual flow follows corpus luteum regression. Our studies of estrogen metabolism in women have indicated that increased destruction of estrogen pertains at the onset of both ovulatory and anovulatory bleeding and may be the precipitating cause of the vascular phenomena which are associated with endometrial breakdown (7). Any effect of ovarian hormones, therefore, upon creatine and creatinine excretion, may depend upon shifts in their metabolism rather than upon the amounts and kinds secreted or administered.

In the various reviews on creatine and creatinine metabolism, the conclusion has been generally reached that fluctuations in the urinary excretion of these 2 compounds by women bear no relationship to the menstrual cycle. This has been based largely on 4 papers (12–15) published between the years 1911 and 1921. Because our own findings do not agree with this conclusion, it seems worthwhile to review these publications in some detail.

Krause (12) in 1911, studied creatine and creatinine excretion in relation to the menstrual cycle in 7 women. In 5 of the 7 cases, only 2 to 4 random specimens were analyzed and in the other 2, upon whom the most work was done (i.e., 14 specimens from each), collections were scattered over a 6-month interval. No urines were obtained during menstruation. It is difficult to draw any conclusions on the basis of such scattered data. Krause's observation, however, that creatine was present in all urines just after menstruation and was absent or present only in traces in most cases 2 or 3 weeks after the period is in general agreement with the findings noted above in our cases in whom creatinuria was followed.

Rose (13) in 1917, studied creatine and creatinine in the urine of 6 normal women, daily specimens being collected from each over 18 to 32-day intervals, including a total of 8 catemenia. She concluded that no correlation exists between menstrual cycles and creatine and creatinine output. From an examination of her figures it is apparent that none of the subjects collected complete 24-hour specimens, since the daily creatinine excretion of each showed such wide fluctuations; in *subject 1* the values varied between 85 and 356 mg. Moreover, the ratios of creatine to creatinine in all of the specimens are very much higher than those found anywhere in the literature on creatine and creatinine excretion, for example, 242 mg. of creatine in a specimen containing only 266 mg. of creatinine. We would be inclined to doubt the value of any conclusions based on data which differ so markedly from those of other investigators.

Rose, Dimmitt and Bartlett (14) in 1918, followed urinary creatine and creatinine daily from 2 normally menstruating individuals for 14 and 13 days, respectively. With one of the subjects, collections started on the day after menstruation ended. Ten of the 14 specimens contained creatine, the largest amount, 160 mg. in 24 hours, occurring in the first specimen obtained just after flow. During the rest of the period studied, the amounts varied between 0 and 70 mg. in 24 hours. Creatinine excretion (1.12 to 1.22 gm. in 24 hours) showed no cyclic variation during these 14 intermenstrual days. The other subject was followed for 13 days starting 3 days before menstruation and including the menstrual specimens. Ten of the 13 specimens contained creatine, the largest amounts (80 and 90 mg. in 24 hours) being found in the 2 immediately premenstrual specimens, the other 11 specimens containing 0 to 60 mg. in 24 hours. Creatinine excretion varied between 0.98 and 1.15 gm. in 24 hours, a definite peak being apparent on the last 3 days before menstruation together with a marked drop at the start of flow. The findings of these 2 cases, therefore, are in general agreement with our observations, although the authors naturally draw no conclusions from such meager data.

Stearns and Lewis (15) in 1921, analyzed the urines of 3 normally menstruating women for creatine and creatinine at frequent intervals throughout a total of 8 menstrual cycles. In the course of this investigation, dietary measures were introduced and both creatine and creatinine were ingested sporadically. The authors concluded that no relationship existed between menstruation and creatine or creatinine excretion. However, in *subject S.*, upon whom the most complete studies were performed, urinary creatine was demonstrable only around the time of the menses in 3 of the 5 cycles followed (except when creatine was ingested). Creatinuria in the absence of creatine ingestion appeared intermenstrually in this subject during 1 cycle when she was "ill and overstrained" and during another when she was on a high-protein diet. During 2 complete consecutive cycles on this subject, when she was in good health and on a normal diet, the curves for both creatine and creatinine excretion, if one omits the values on those days when creatine or creatinine were ingested, are entirely similar to those on *O. W. S.* above.

The results on the 6 women studied by us, therefore, confirm findings recorded by previous investigators. It is possible that in some women fluctuations in creatine and creatinine excretion occur which are not related to menstruation and which would obscure the menstrual changes or make them seem of no significance. The repeated observation, however, both in our own data and those of others, that menstruation is associated with an increased creatinuria and a drop in creatinine excretion would appear to be indicative of some relationship between menstruation and creatine and creatinine metabolism.

The values for 24-hour creatinine excretion on these 6 menstruating women are summarized in table 2. The data illustrate the degree of fluctuation in creatinine output which may be expected in normally menstruating women. In no instance was the

coefficient of variation greater than 10.9% or the maximum deviation from the mean value greater than 21.4%.

Creatinine Excretion in Women with Gynecological Disorders

Effect of hormone administration. Five women with various menstrual abnormalities have been followed, in 4 of whom the effect of hormone administration has been observed. The estrogenic and gonadotropic potencies of the urines were measured as well as the creatinine content.

Seven consecutive specimens were studied from *Mrs. A. M.*, aged 32, a case of amenorrhea of 8 years' duration. The patient weighed 93 pounds. The creatinine varied over rather narrow limits (0.78 to 0.91 gm. in 24 hours) and bore no relationship to rather marked fluctuations in the levels of follicle-stimulating hormone (0 to 90 R.U. in 24 hours) and of total estrogen (75 to 250 I.U. in 24 hours).

Six specimens were analyzed from *Miss M. C.* during the years 1936 to 1941, complete hysterectomy with castration having been performed in 1933. The 4 specimens collected when no hormones were being administered, the last on Feb. 6, 1941, contained 1.20 to 1.27 gm. of creatinine, 30 to 50 I.U. of total estrogen and around 100 R.U. of follicle-stimulating hormone (FSH) per 24-hour volume. Five mg. of estrone (50,000 I.U.) in oil were injected intramuscularly on Feb. 10, 1941. The 2 specimens collected immediately thereafter contained 2,450 and 400 I.U. of total estrogen, respectively, no demonstrable FSH, and 1.27 and 1.21 gm. of creatinine per 24-hour volume. It is apparent that creatinine excretion, within the time limits of this experiment, was not affected by this large single injection of estrone, despite the marked changes in hormone output.

Mrs. M. S., a sterility case with irregular and scanty catamenia, was followed during a 41-day cycle (14 specimens), on the 33rd day of which a single injection of pituitary gonadotropin[2] was given intravenously. From the clinical data together with the curves of hormone excretion, we believe that a beginning pregnancy may have been interrupted by the injection. On *days 31* and 33 the tests for urinary FSH gave positive pregnancy reactions, no gonadotropic activity having been previously demonstrable. An endometrial biopsy on the day before flow, which was profuse, showed early decidua. Urinary estrogens varied between 300 and 1,650 I.U. per 24-hour volume, the curve of excretion being entirely similar to that shown during what may have been a spontaneous early abortion in *L. D. Y.* (fig. 2). The curve for urinary creatinine, with values between 1.20 and 1.53 gm. in 24 hours, was suggestive of the 2-peak type, although less uniform than those recorded above. No correlation was apparent between creatinine excretion and the injection of the pituitary gonadotropin extract, but a drop in creatinine excretion accompanied the onset of flow.

TABLE 2. CREATININE EXCRETION IN 6 MENSTRUATING WOMEN

Subject	No. of Specimens	No. of Cycles	Range of Values	Mean Value and Std. Dev.	Coef. of Var.	Maximum Deviation	
			gm./24 hr.	*gm./24 hr.*	%	gm.	%
E.E.J.	21	2	1.21–1.69	1.45±0.12	8.3	0.24	17.5
O.W.S.	60	6	1.32–1.71	1.48±0.09	6.0	0.23	15.5
L.D.Y.	20	3	1.12–1.48	1.31±0.13	9.9	0.19	14.5
H.S.[1]	6	1	1.00–1.14	1.05±0.05	4.8	0.09	8.5
L.G.	9	1	1.00–1.33	1.19±0.13	10.9	0.19	15.9
S.S.[2]	24	1	0.80–1.08	0.89±0.08	9.0	0.19	21.4

[1] Based on analyses of 48-hour volumes of urine.
[2] Based on analyses of 8-hour specimens collected from 11 P.M. to 7 A.M.

The data on *Mrs. A. G.*, a case of obesity (weight 239 lb.) and marked masculine hirsutism, with long intervals of amenorrhea, are presented in figure 3. Over a period of 6 weeks, 5 intravenous injections of pituitary gonadotropin were given. Endometrial biopsies, which in 4 of 6 instances were followed by bleeding of 2 to 7 days' duration, showed both before and during injections the same picture, namely, early proliferation. Each injection was followed by a marked rise in estrogen excretion. Urinary FSH was demonstrable on 3 occasions, once before and twice during injections. The fluctuations in urinary creatinine bore no apparent relationship either to the injections, the estrogen and FSH excretion or to the endometrial bleeding.

Mrs. B. V. A., a case of typical functional uterine bleeding, was studied over a 7-year interval, during which time the effects of chorionic gonadotropin,[3] progesterone, estrone and estriol administration were investigated. Of the 24 specimens analyzed, the creatinine values of 10 have had to be discarded, since the accuracy of hospital collections could not be relied upon except when a retention catheter was employed. However, there is sufficient data to indicate that neither chorionic gonadotropin[3] (5 cc. daily on 3 successive days), progesterone (30 mg. over 3 days on 1 occasion and 75 mg. over 3 days on another), estrone (100,000 I.U. over 2 days), nor estriol (0.5 to 2.0 mg. by mouth daily for 3 months) had any significant effect

[2] Gonadotropic extract of sheep pituitaries, (Prephysin) Chappel Laboratories, Rockford, Illinois.

[3] Chorionic gonadotropin (Antuitrin-S), Parke, Davis and Company, Detroit, Michigan.

upon creatinine excretion. Despite the marked effect of these hormones upon the endocrine balance, as evidenced by the changes in estrogen excretion following therapy, the range of creatinine values when the patient was receiving no hormones were practically the same (0.83 to 1.03 gm. in 24 hours in 8 specimens) as when they were being administered (0.88 to 1.04 gm. in 24 hours in 6 specimens). Creatinine excretion in this woman also bore no apparent relationship to menstrual flow, the range of values being the same whether the patient was bleeding profusely, staining or was in an amenorrheic stage.

It is conceivable that if creatine determinations had been performed upon the specimens from these women to whom hormones were administered, some more definite effect upon creatine and creatinine metabolism might have been apparent. Beard (16), for example, found creatinine output of this individual, although Koven and Beard (19) observed an initial increase followed by a decrease in urinary creatinine following progesterone administration to normal rats.

Schrire and Zwarenstein (20) found that chorionic or pituitary gonadotropic extracts produced an increased creatinine output in normal rabbits but had no effect upon the already high creatinine excretion of castrates. Three of our subjects, none of whom was castrated, received gonadotropic extracts. In *Mrs. M. S.* a single intravenous injection of a potent pituitary preparation during the cycle of probable conception was followed by a continued rise in estrogen excretion, after which there was a precipitous drop and bleeding. No change in creatinine output could be correlated with the injection. *Mrs. A. G.*, who received 5 intravenous injections of this same prep-

TABLE 3. CREATININE EXCRETION IN 5 WOMEN WITH GYNECOLOGICAL DISORDERS (4 of these were treated with sex hormones). Demonstrating that creatinine excretion is as constant under these conditions as in normally menstruating women (cf. Table 2)

Subject	Clinical Condition	No. of Specimens	Dates of Specimens	Hormonal Treatment	Range of Values	Mean Value	Stand. Dev.	Coef. Var.	Maximum Deviation	
					gm./24 hr.	*gm./24 hr.*	*gm.*	%	*gm.*	%
A M.	Complete amenorrhea	7	11/2–9/34	0	0.78–0.91	0.81	0.05	6.3	0.10	12.3
A.G.	Sterility, obesity, hirsutism	15	7/5–9/13/35	Pit. gonadotropin	1.89–2.32	2.11	0.17	8.0	0.22	10.4
M.C.	Menopause	6	1936–1941	Estrone	1.20–1.27	1.24	0.03	2.4	0.03	2.4
M.S.	Conception and early abortion	14	6/25–8/9/35	Pit. gonadotropin	1.20–1.53	1.36	0.11	8.1	0.17	12.5
B.V.A.	Metrorrhagia	14	1934–1941	Ch. gonadotropin, progesterone, estrone, estriol	0.83–1.04	0.95	0.07	7.4	0.12	12.6

that the injection of male and female sex steroids into rats resulted in an increased creatinuria, while no definite effect upon creatinine excretion was demonstrable. Williamson and Gulick (17), working with male rabbits, found that testosterone raised muscle creatine and decreased creatinuria, whereas, within the time and dosage limits of their experiments, creatinine metabolism was not affected.

Sharpey-Schafer and Schrire (18) reported that large daily injections of estradiol benzoate (100,000 I.U.) or of diethylstilbestrol (10 mg.) had no effect upon creatinine excretion in normal women but decreased the 24-hour output in menopausal women and castrates. In *M. C.*, the castrate in our series, we observed no such effect, although hormone excretion was markedly altered. However, only a single injection of 5 mg. of estrone was given. *B. V. A.*, the case of functional bleeding, received larger amounts of estrogen over longer periods with no significant effect upon creatinine excretion, although marked increases in estrogen output resulted. Furthermore, large daily injections of progesterone (10 to 25 mg.) temporarily stopped excessive bleeding and decreased the rate of estrogen destruction but did not demonstrably alter the aration over a 6-week interval, during which no ovulation occurred, showed marked fluctuations in estrogen excretion related to the injections but no consistent change in creatinine output. With *Mrs. B. V. A.*, excessive flowing ceased and estrogen output increased with chorionic gonadotropin injections but urinary creatinine was not demonstrably affected.

Our observations were incidental to the study of female sex hormone metabolism and may not be interpreted as signifying that creatinine metabolism is uninfluenced by sex hormone administration in women. They do indicate, however, that amounts of these hormones sufficient to cause physiological changes in women and markedly to affect hormone excretion do not result in any consistent or significant changes in creatinine output. Any fluctuations in creatinine excretion which followed hormone administration probably did not result from the hormones, since the range of these fluctuations was no greater than that observed in the same individuals when no hormones were being given. Moreover, in the sum-

TABLE 4. CREATININE EXCRETION IN 10 NORMALLY PREGNANT WOMEN

	Stage of Pregnancy	No. of Specimens	Range of Values	Mean Value and Std. Dev.	Coef. of Var.	Maximum Deviation	
	weeks		*gm./24 hr.*	*gm./24 hr.*	*%*	*gm.*	*%*
L.D.Y.	5–37	11	1.11–1.45	1.31±0.11	8.6	0.20	15.3
O.W.S.	5–33	6	1.30–1.72	1.50±0.14	9.3	0.26	17.4
E.B.F.	16–39	10	0.86–1.19	0.98±0.10	10.2	0.21	21.5
P.P.	26–term	13	1.04–1.41	1.17±0.10	8.5	0.24	20.5
C.P.	12–38	6	1.00–1.34	1.20±0.15	12.5	0.20	16.6
A.P.	12–39	7	1.14–1.51	1.31±0.13	9.9	0.20	15.3
R.C.	26–term	12	1.22–1.76	1.40±0.16	11.4	0.35	25.0
G.R.W.	10–31	6	0.81–1.15	0.96±0.10	10.4	0.19	19.8
D.L.	7–26	5	1.14–1.37	1.28±0.09	7.0	0.14	10.9
D.G.	18–38	4	1.15–1.42	1.30±0.11	8.4	0.15	11.6

mary of creatinine results on nonpregnant women presented in tables 2 and 3, it is apparent that the coefficients of variation and the maximum deviations from the mean values in those women to whom hormones were administered are no greater than in those who received no injections.

Creatinine Excretion During Conception and Threatened Abortion

Two cases, *L. D. Y.* and *M. S.* were followed through what appeared to be the period of conception with abortion prior to the second missed period. In both, a drop in creatinine excretion preceded flow and seemed to be more directly associated with bleeding than with estrogen excretion. The results in a third patient, *Mrs. Y B.*, are presented in figure 4 and include observations over the last 10 days prior to the cycle of conception and the first 54 days of a pregnancy complicated by threatened abortion. Hormone excretion was followed during this interval and also throughout the rest of pregnancy, which was normal. The 5 specimens collected before the last catamenia showed a late cycle peak in creatinine excretion and a drop before and at the onset of flow. (This constitutes the 8th case and the 16th cycle in which this change in creatinine excretion has been observed in association with menstruation.) During the month of conception, although estrogen excretion followed the curve indicative of ovulation, there was no peak and drop in creatinine. There was, however, a peak in creatinine excretion on the 35th day followed by a marked drop prior to an episode of staining on the 41st and 42nd days. This rise and fall in creatinine excretion again occurred preceding a second and more alarming episode of staining at the time of the second missed period.

The findings in this case indicate again that, although there is no direct relationship between ovarian activity and creatinine excretion, some change in creatinine metabolism is associated with uterine bleeding. The marked hormonal changes which accompany early pregnancy (chorionic gonadotropin was excreted by this woman in rapidly increasing amounts between the 35th and 54th days) did not affect the levels of creatinine. The average creatinine excretion during the 10 days before the cycle of conception was 0.98 gm. in 24 hours with a coefficient of variation of 7.1%. The mean value of the 22 specimens collected during the first 54 days of pregnancy was 0.94 gm. in 24 hours with a coefficient of variation of 8.5%.

Creatinine Excretion During Normal Pregnancy

Ten women carefully instructed and trained in the accurate collection of 24-hour volumes of urine have been followed with repeated specimens during pregnancy, a total of 80 determinations. In these 10 normal cases, urinary pregnanediol, estrogens and chorionic gonadotropin followed the general curves

TABLE 5. CREATININE EXCRETION IN 4 WOMEN DURING FIRST AND SECOND STAGES OF LABOR

Subject	Creatinine Excretion before Labor			Creatinine Excretion during Labor	
	Stage of pregnancy	No. of specimens	gm./24 hr.	Hours of labor covered	gm./24 hr.
R.C.	26 wk. to term	12[v]	1.22–1.76	1st 6[v]	1.33
	1 wk. before labor	1[v]	1.30	6th to 13th[v]	0.98
				13th to 20th[v]	1.12
				20th to 30th[v]	0.97
				30th to 37th[v]	1.02
				37th to 41st[v]	0.76
				last 5 of 46-hr. labor[c]	0.61
P.P.	26 wk. to term	13[v]	1.04–1.41	1st 6[v]	1.20
	3 days before labor	1[v]	1.25	6th to 12th[v]	1.30
				12th to 20th[v]	0.80
				last 6 of 26-hr. labor[c]	0.79
A.C.	36 to 12 hr. before mechanical induction	1[v]	1.08		
	last 12 hr. before induction	1[v]	1.02		
	(labor started immediately after artificial rupture of membranes)			1st 2[c]	0.57
				last 3 of 5-hr. labor[c]	0.65
P.L.	(not followed before labor started)			1st 2[c]	1.02
				3rd to 5th[c]	1.03
				7th to 9th[c]	0.77
				last 6 of 23-hr. labor[c]	0.63

[v] Voided specimen.
[c] Catheter specimen.

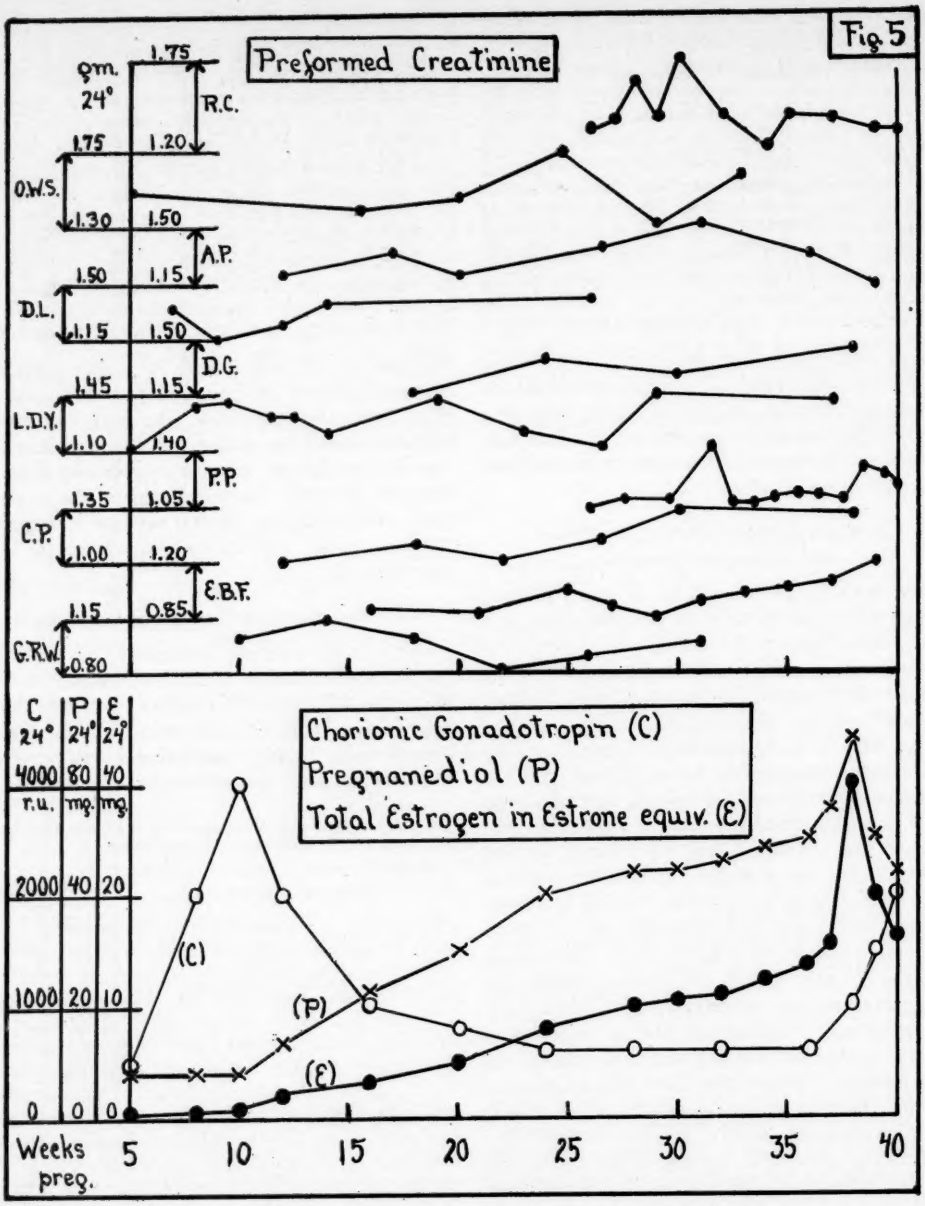

FIG. 5. Creatinine excretion during 10 normal pregnancies together with composite curves of hormone excretion throughout normal pregnancies.

previously published by us (4, 5, 11) and graphically presented in the lower part of figure 5, although the actual levels of excretion varied with individuals. The fluctuations in creatinine excretion were of the same order as those observed in nonpregnant women and bore no apparent relationship to the endocrine balance as reflected in hormone excretion. The results are summarized in figure 5 and table 4.

Two of these women (*O. W. S.* and *L. D. Y.*) had also been studied when not pregnant. It is interesting to note (tables 2 and 4) that their mean values of creatinine excretion as well as their coefficients of

variation and maximum deviations from the mean were the same in the pregnant as in the nonpregnant state. Considering the tremendous hormone changes that take place during pregnancy, this observation argues against any direct effect of the female sex hormones upon creatinine excretion.

Creatinine Excretion During Labor

Urinary estrogens, pregnanediol and creatinine have been measured in repeated specimens from 4 women during labor. An inlying catheter was employed in 2 of them; collections from the other 2 were personally supervised by the writer. The results on urinary estrogens and pregnanediol indicated that labor contractions in all, in 1 of whom labor was induced, were accompanied by a progressive and rapid decrease in hormone excretion together with a sudden marked increase in the rate of sex steroid destruction (11). The creatinine values (table 5), based on 2 to 10-hour specimens, are all expressed in terms of 24-hour excretion for the sake of comparison. There was in each case a 34 to 54% decrease in the rate of creatinine excretion between the onset of labor and delivery, this being the most marked change in creatinine output that we have encountered in our observations upon pregnant and nonpregnant women.

It is impossible to explain the significance of this finding, especially since neither the creatinine content of the blood was followed nor was urinary creatine measured. However, it is sufficiently striking to indicate that some marked change in creatinine metabolism accompanies labor and delivery. There is no experimental indication that muscular exercise would result in a decrease in urinary creatinine; in fact, there is convincing evidence that muscular exercise temporarily increases the rate of creatinine excretion (21, 22). We would consider the striking drop during labor as similar to the observations reported above at the time of menstruation and due to similar through as yet undetermined causes. The same hormonal changes which characterize menstruation (6) pertain, on a larger scale, during labor and delivery (11). It seems likely that the circulatory changes, vasoconstriction and increased capillary permeability with concomitant water and salt retention, which we know are associated with the menstrual phenomenon and with changes in sex hormone metabolism, are also associated with labor and delivery and might well affect creatine and creatinine metablism.

TABLE 6A. CREATININE EXCRETION IN 9 WOMEN WHO HAD OR DEVELOPED PREËCLAMPSIA DURING PERIOD OF STUDY (to 6 of these sex hormones were administered). Comparison of values during normal, pathological and experimental conditions

Subject	Clinically Normal			Showing Clinical Manifestations of Preëclampsia						
				No hormones administered			During hormone administration			
	Weeks pregnant	No. of spec.	Range of values	Weeks pregnant	No. of spec.	Range of values	Hormonal R[1]	Weeks pregnant	No. of spec.	Range of values
			gm./24 hr.			*gm./24 hr.*				*gm./24 hr.*
M.P.	10 to 36	5	0.97–1.06	36 to 38	3	0.87–1.14				
W.H.	25 and 28	2	1.29–1.43	34 and 36	2	1.31–1.41				
R.W.	31 and 34	2	0.94–1.00	34½	1	1.00				
G.K.	22 to 31	6	0.91–1.05				E.B. (10)+T. (25)	32 to 37	8	0.83–1.09
M.L.	26 to 32	5	1.05–1.20	32 to 33	4	0.88–1.09	P.G. (5 cc.)	33 to 35	9	0.88–1.27
J.K.	27 and 28	2	1.33–1.42				Stilbestrol (40)	29 to 30	3	1.33–1.44
							E.B. (10)+P. (20)	31 to 37	4	1.37–1.45
R M.				36 to 37	3	0.94–1.23	E.B. (10)+P. (50)	37 to 39	4	0.93–1.01
H.H.				34 to 35	3	0.92–1.12	E.B. (10)+P. (50)	35 to 37	5	0.94–1.05
V.M.				34 to 36	6	1.26–1.45	P.G. (5 cc.)	36 to 37	4	1.25–1.53

[1] E.B., estradiol benzoate; T., testosterone propionate; P., progesterone. Figures in parentheses, mg. injected daily. P.G., Pituitary gonadotropic factor (Prephysin, Chappel); 5 cc. (marked 125 U.) given daily.

Creatinine Excretion in Women With Preëclampsia

Effect of hormone administration. The data on 9 preëclamptics, 6 of whom were followed prior to the

onset of toxic manifestations and to 6 of whom hormones were administered, are summarized in tables 6, *A* and *B*. In all of the first 6 individuals, hormone studies prior to the onset of clinical abnormalities gave evidence of an abnormal rise in serum chorionic gonadotropin and a gradual decrease, rather than the normal increase, in serum estrogen and the levels of estrogens and pregnanediol in the urine. In each case, toxic manifestations were accompanied by a marked increase in the rate of steroid destruction (8). There was no indication, however, that any consistent change in creatinine excretion either preceded or accompanied the hormonal and clinical abnormality. There was also no apparent correlation between the fluctuations in creatinine excretion and either the clinical or endocrine changes which followed injections. In table 6, *B*, the creatinine data on the 8 preëclamptic patients from whom a total of 4 or more specimens were collected are summarized. It is apparent that the coefficients of variation and the maximum deviations from the mean values in these women, to 6 of whom large daily doses of hormones were given, are no greater than those encountered in normally pregnant women (table 4).

The hormonal changes which precede and accompany the onset of preëclampsia are entirely similar to those which occur after the onset of labor and which characterize the menstrual phenomenon. In the latter two situations we have evidence that creatine and creatinine metabolism are affected, whereas the data of tables 6, *A* and *B*, indicate that a similar situation in preëclampsia does not affect creatinine excretion. This may be accountable to the fact that the changes during labor and at the onset of menstruation take place over a comparatively short interval, whereas in the preëclamptic individual similar changes are going on over a period of weeks before the toxemic condition becomes clinically apparent. In the above case of functional uterine bleeding (*B. V. A.*) the same type of estrogen degradation pertained whether the patient was in a bleeding or an amenorrheic stage, the flowing, unlike normal menstruation, being gradual rather than sudden in its onset. Furthermore, in those patients in whom hormone administration appeared to shift the hormonal and clinical abnormality in the direction of normal, the effect was by no means spectacular, but took place gradually over a 6-day or longer interval of daily injections. It is entirely possible that any influence upon creatine and creatinine metabolism would depend upon the rapidity with which the causative metabolic shifts take place.

Creatinine Content of Urine as a Gauge of Accuracy of Collections and Basis for Calculated 24-Hour Volumes

The data presented demonstrate, as has been noted by others, (22, 23, 24) that the 24-hour excretion of creatinine by any individual is only relatively constant. The largest coefficient of variation observed in any woman of our series has been 12.5% and the greatest maximum deviation from the mean 25%. In general, both values have been considerably lower than these figures. Various physiological, pathological and experimental conditions do not appear to affect the range of values for any individual, the only exception to this statement being the marked decrease in the rate of creatinine excretion during labor. When repeated specimens from an individual are being analyzed, therefore, the finding of a 24-hour creatinine value more than 25% higher or lower than the average for that individual would seem to warrant the assumption (unless the patient is in labor) that an error in collection has been made. In fact, any value under 0.80 gm. in 24 hours is open to suspicion.

In table 7 we have analyzed representative data demonstrating the gross errors that may be expected under ordinary hospital conditions. The results on *B. V. A.* are particularly revealing, since the 10 hospital collections may be compared with 14 other specimens from this same individual which we know were reliable (see table 3), 5 while she was on con-

TABLE 6B. SUMMARY OF DATA OF TABLE 6A, DEMONSTRATING THAT CREATININE EXCRETION IN PREËCLAMPTIC WOMEN TO WHOM SEX HORMONES ARE ADMINISTERED IS AS CONSTANT AS IN NORMAL PREGNANCY (CF. TABLE 4)

Subject	Stage of Pregnancy	No. of Specimens	Range of Values	Mean Value and Std. Dev.	Coef. of Var.	Maximum Deviation	
	weeks		*gm./24 hr.*	*gm./24 hr.*	*%*	*gm.*	*%*
M.O.	10 to 38	8	0.87–1.14	1.03±0.08	7.7	0.16	15.5
W.H.	25 to 36	4	1.29–1.43	1.36±0.07	5.1	0.07	5.1
G.K.	22 to 37	14	0.83–1.09	0.99±0.09	9.1	0.16	16.2
M.L.[1]	26 to 35	18	0.88–1.27	1.05±0.10	9.5	0.22	20.9
J.K.	27 to 37	9	1.33–1.46	1.39±0.05	3.6	0.07	5.1
R.M.	36 to 39	7	0.93–1.23	1.05±0.11	10.5	0.18	17.1
H.H.	34 to 37	8	0.92–1.12	1.00±0.07	7.0	0.08	8.0
V.M.[1]	34 to 37	10	1.25–1.53	1.37±0.09	6.6	0.16	11.7

[1] Based on analyses of 12-hr. specimens collected from P.M. to A.M.

stant drainage and 9 which she collected herself at home. Despite the fact that special nurses were assigned to this case for the sake of obtaining accurate collections of urine, the coefficient of variation and the maximum deviation from the mean on the 10 hospital specimens were both nearly 3 times as high as those on the 14 reliable 24-hour volumes. Actually, the error was even greater than would appear from the figures, since we may assume that the true mean value for the hospital voidings was about 0.95 gm. of creatinine in 24 hours rather than 0.74 gm. This would give a coefficient of variation of 28% and a maximum deviation of 48%. In other words, if we had not performed creatinine determinations and had accepted the volumes received as true 24-hour collections, we would have introduced into our studies of hormone excretion possible errors 4 times as great, according to the reliable data on this patient (table 3), as those that may have resulted from recalculating 24-hour volumes on the basis of creatinine content.

The other 6 patients in table 7 were followed while in the toxemic ward of a large obstetrical hospital. Written orders were given and directions posted for the accurate collection of 24-hour volumes. The maximum deviations from the mean vary between 51 and 86% and the coefficients of variation lie between 30 and 48%. A comparison of these figures with those in tables 2, 3, 4 and 6, *B* demonstrate the magnitude of the errors that may be introduced by inaccurate collections. Here again these figures, must underestimate the true errors, since the low mean values on these patients indicate that most of the mistakes were due to loss of urine and that the average daily excretion of creatinine for each individual was probably closer to the highest figure in the range of values. On this basis the maximum deviations would be 80 to 115% as compared with 5 to 25% in the reliable collections from pregnant women. In such cases, where no known reliable collections have been available, we have had to assume a creatinine coefficient for the individual being studied and recalculate, on the basis of this assumed figure, a corrected 24-hour volume for all specimens according to their creatinine content. Although this procedure is open to criticism, it at least gives comparable day to day values of hormone excretion and is certainly preferable to accepting volumes as received from any ordinary hospital ward.

Even when a patient has private nursing care, errors appear to be unavoidable and for this reason some check on the accuracy of every 24-hour volume is absolutely essential when quantitative urinary studies are being conducted. We have found that individual patients are for the most part very conscientious about collections provided they are given full and careful instructions. Whenever possible, we have had patients supervise their own collections while in hospitals.

We have found hospital specimens more accurate if only 12-hour volumes from 7 P.M. to 7 A.M. are followed, since during these hours there are fewer voidings, less general activity in the ward and fewer nurses on duty. (In studying estrogen and pregnanediol excretion, this is possible only in pregnant women, since 24 to 72-hour volumes are required from nonpregnant patients in order to get enough material for accurate assay.) Comparison of the day and night excretion of creatinine in a number of our patients has shown that, although some women excrete more creatinine at night than during the 12-hour day period and others excrete less, 12-hour values are as constant as 24-hour amounts, provided collections on a given individual always cover the same 12-hour interval. This observation has been reported by others (22, 23, 25). Bachman (26) has recently shown that the rate of pregnanediol excretion and of the 17-ketosteroids does not vary from day to night and is not affected by the volume of urine excreted.

TABLE 7. CREATININE EXCRETION BASED ON 24-HOUR VOLUMES AS RECEIVED FROM HOSPITALIZED PATIENTS; DEMONSTRATING THE GROSS ERRORS INTRODUCED THROUGH INACCURATE COLLECTIONS

(Compare with tables 2, 3, 4 and 6B.)

Subject	Clinical Notes	No. of Specimens	Range of Values	Mean Value and Std. Dev.	Coef. of Var.	Maximum Deviation	
			gm./24 hr.	*gm./24 hr.*	%	*gm.*	%
B.V.A.[1]	Metrorrhagia *Preëclampsia*	10	0.49–0.98	0.74±0.16	21.6	0.25	33.8
A.D.[2]	33–34 wk.	8	0.39–0.98	0.65±0.25	38.4	0.33	51.0
J.E.[2]	33–38 wk.	9	0.30–0.92	0.66±0.20	30.3	0.36	55.0
L.S.[2]	30–32 wk.	10	0.39–1.32	0.80±0.32	40.0	0.52	65.0
M.B.[2]	30–34 wk.	9	0.40–1.20	0.79±0.34	43.0	0.41	52.0
A.G.[2]	36–38 wk.	11	0.13–1.60	0.90±0.43	47.8	0.77	86.0
R.C.[2]	35–37 wk.	9	0.45–1.55	1.03±0.31	30.1	0.58	56.0

[1] Patient under private nursing care; written orders given for 24-hour urine collection.
[2] Patients on ward service; written orders given for 24-hour urine collections.

Our own studies (unpublished data) confirm this observation for pregnanediol and show that the same constancy in rate of excretion applies to the estrogens. It would appear, therefore, that the analysis of 12-hour rather than 24-hour volumes is a perfectly reliable procedure. Under no conditions, however, have we ever felt justified in omitting creatinine determinations as a check on the accuracy of hospital collections.

SUMMARY AND CONCLUSIONS

The 24-hour excretion of preformed creatinine has been measured in 6 menstruating women (140 determinations during 14 cycles); in 5 women with gynecological disorders to 4 of whom estrogenic, progestational or gonadotropic hormones were administered (56 determinations); in 1 woman before and during the cycle of conception and during the first 2 months of a pregnancy complicated by threatened abortion (27 determinations); in 10 women during the course of normal pregnancy (80 determinations); in 4 women during labor (19 determinations); and in 9 women who developed preëclampsia, to 6 of whom large amounts of estrogen, progestin, testosterone or pituitary gonadotropic hormone were administered (81 determinations). Urinary creatine has been measured in 4 of the menstruating women (113 determinations during 11 cycles). Urinary estrogens (either total or separated) were also measured in all specimens, the gonadotropic potency of the urine in many and urinary pregnanediol in those from pregnant women.

In menstruating women there was evidence that, although ovarian secretion did not directly affect creatine and creatinine excretion, a definite change in creatine and creatinine metabolism was associated with the menstrual phenomenon itself.

Neither gynecological disorders nor the administration of hormones to nonpregnant women in amounts sufficient to cause physiological changes and markedly to affect hormone excretion, appeared to influence the creatinine output.

The only consistent or significant change in urinary creatinine in normal pregnancy was found during the course of labor, when a striking drop in the rate of its excretion was encountered.

Creatinine excretion was not demonstrably affected by the development of preëclampsia despite the accompanying marked changes in hormone metabolism, or by the large amounts of sex hormones administered to patients with the disease.

From the data presented we are led to believe that any effect of female sex hormones upon creatine and creatinine excretion may depend upon rapid shifts in sex steroid metabolism and accompanying rapid changes in vascular supply and in water and salt balance, rather than directly upon the amounts and kinds of hormones secreted or administered.

Under all of the conditions investigated, except during labor, creatinine determinations were found to provide a satisfactory gauge of the accuracy of 24-hour collections. Any value of less than 0.8 gm. in 24 hours may be considered open to suspicion and the finding of a 24-hour creatinine value more than 25% higher or lower than the average for a given individual appears to warrant the assumption that an error in collection has been made.

The most dependable collections are made by carefully instructed patients, either at home or when supervising their own hospital collections. Ward specimens are extremely unreliable and even with special nursing care gross errors appear to be unavoidable. The collection of 12-hour rather than 24-hour amounts reduces these errors. Recalculation of the 24-hour volumes of specimens in which gross errors are apparent, on the basis of the creatinine concentration and an assumed or known average 24-hour creatinine output for a given individual, greatly reduces the inaccuracy of results. Some check on the accuracy of collections is an essential part of any quantitative urine analysis.

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Creatine Retention Capacity of Boys in Relation to Androgen Function[1, 2]

[Androgens and Creatine Metabolism]

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IT IS KNOWN that prepuberal boys and girls and adult women exhibit a creatinuria though the adult male does not. Also that the tolerance for exogenous creatine is much less in the former group than in the adult male. The difference in tolerance between the sexes is, apparently, not due to a difference in sex, per se, since some muscular women exhibit a marked capacity to retain exogenous creatine (1).

It is believed that a poor creatine tolerance occurs until about the age of 13 years and parallels the physiological creatinuria of adolescence (2).

Castrates, eunuchoids, aged humans and those exhibiting hypogonadism also show impaired creatine retention. Thus interest is focused on the relation of hormones to the metabolism of creatine. Remen (3) found a creatinuria in elderly men (70–90 years), one eunuch and one castrate. These behaved like infants and children in that they excreted most of the injected creatine. Thus he concludes the male gonad has a definite effect on creatine excretion.

Sutton (4) reports a retention of exogenous creatine in prostatics (52–68 years) and nonprostatics (54–77 years) comparable to that of young men (24–37 years). This retention of exogenous creatine was not increased in normal young males or elderly prostatics by administering 200 mg. of testosterone propionate in divided doses.

Schittenhelm and Buhler (5) found a spontaneous creatinuria in diseases of the pituitary, thyroid and gonads. Patients with gonad insufficiencies excrete more exogenous creatine than do patients with other conditions. Thus the gonad has important function in that it can prevent creatinuria and when gonadal function is lost, creatinuria occurs.

That there is a definite relation between the hormones and the metabolism of creatine has been shown by many recent workers. While much of the experimental work points to an increased creatine tolerance and a reduction of creatinuria brought about by the administration of certain hormones, the opposite has also been reported.

Kun and Peczenik (6) have induced a creatinuria in rats castrated postpuberally which they were able to suppress by administration of urinary androgen.

Coffman and Koch (7) found the creatinuria of the control period following castration to be small. Exogenous creatine, however, produced an intense creatinuria which could be suppressed by injections of testosterone propionate.

Kenyon et al. (8) reduced the creatine excretion in a eunuchoid, intensified by exogenous creatine, by the daily administration of testosterone propionate.

Koven and Beard (9) and Pizzolato and Beard (10) observed a creatinuria in rats following castration. They also report a creatinuria following injection of anterior pituitary extracts, estrogen, testosterone, cortin and saline and water.

In relation to the young age-group Buadge (11) claimed that male hormone stops the creatinuria of childhood while female hormone increases it. Buhler (12) reported that neither estrogen nor androgen had any effect in increasing creatine tolerance in childhood.

Jailer (13) was able to abolish the creatinuria of young male monkeys and increase their capacity to retain exogenous creatine by the administration of testosterone propionate. Castration in mature monkeys resulted in an increased creatinuria and impaired creatine retention. The injection of testosterone propionate abolished the creatinuria of castration and restored the capacity to retain creatine. Estradiol benzoate had no effect on creatine excretion. None of the procedures produced any effect on creatinine excretion

EXPERIMENTAL PROCEDURE

The experiments here reported are concerned with the relation of chorionic gonadotropic hormone[3] and

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[2] Presented in partial fulfillment of the degree of Doctor of Medical Science, College of Physicians and Surgeons, Columbia University, New York City.

TABLE 1. EFFECT OF CHORIONIC GONADOTROPIN ON CREATINE RETENTION IN BOYS

Patient Age	Control Period			After Gonadotropin Injection			
	Creatinine	Creatine[1]	C.R.T.[2] (excretion)	R.U. administered	Creatinine	Creatine[1]	C.R.T.[2] (excretion)
	mg.	mg.	%		mg.	mg.	%
R.R., 5 yr.	353	287	69	5500	349	182	65 83
G.B., 7 yr.	436	129	77 99	8800	536	98	82 91
S.Z., 8 yr.	455	74	55 75	2500	487	220	73 84
K.J., 8 yr.	365	48	51 66	8500	776	154	96 100
G.F., 9 yr.	505	214	61 91	6050	621	66	65 96
J.C., 10 yr.	433	143	67 86	4200+	533	337	65 89
C.L., 10 yr.	523	285	44 98	6500	587	201	81 100
D.K., 10 yr.	566	101	43 56	3000	864	116	41 52
L.T., 11 yr.	877	131	36 38	5450	819	29	26 28
A.P., 14 yr.	646	194	68 —	1800	679	250	65 79

[1] As creatinine.
[2] Creatine retention test.

androgenic hormone[4] to creatine metabolism in young males. Eighteen subjects were used, with each serving as his own control. These patients were kept on a meat-free diet the day preceding, during, and the day following that of creatine feeding. Twenty-four hour samples of urine were analyzed for creatinine and creatine following the methods of Folin (14) and the modification of Benedict and Myers (15) respectively. The urines were tested for sugar and acetone at various intervals since these interfere with the Jaffe reaction.

The creatinine values were expressed in milligrams and the creatine in milligrams of creatinine. Five consecutive 24-hour samples were used. Two grams of creatine hydrate were given on the morning of the 4th day. The 5th sample was collected in order to have a determination of the excretion of exogenous creatine in 48 hours.

Following this control series the patients were given a course of gonadotropic factor intramuscularly (200 R.U. 3 times weekly) and the above tests repeated.

Then following a rest period, a course of testosterone propionate (25 mg. 3 times weekly intramuscularly) was given and the tests again repeated.

Creatine excretion in immature males. Immature males show a creatinuria of varying degree. When given creatine retention tests a high percentage of the exogenous creatine is excreted in the urine. In the above tests the average excretion in 24 hours during the control series was 67% of the ingested creatine. This was the average of an actual variation ranging from 43 to 84%. Fifty-six to 99% of the creatine was excreted in the 48-hour period following the ingestion of 2 gm. of creatine hydrate.

Following the injection of gonadotropin as illustrated in table 1 the average excretion (omitting *case L. T.*) in 24 hours was 70%. The actual excretion varied from 41 to 96%. In the case of *case L. T.* the excretion was low both during the control period and following gonadotropic therapy with no appreciable change being produced by the hormone.

Similarly, following the administration of androgen (table 2) the excretion of exogenous creatine was high. Again omitting *case L. T.* and also *case A. G.* the average excretion in 24 hours was 83%. The actual excretion varied from 69 to 100%.

With the exception of *case A. G.* it would seem that the injection of gonadotropic or androgenic hormones, in the doses illustrated produces no increase in creatine retention and, in many cases, there is an actual decrease, i. e., an increase in the excretion of exogenous creatine.

Case A. G., who showed an increased retention of exogenous creatine following androgen therapy, was an obese 9-year-old male of the Fröhlich type whose B.M.R. was −24%. The left testicle was normally placed in the scrotum, the right was palpable in the upper canal and atrophic. Secondary sexual changes were present in this boy (rather marked growth of suprapubic hair and palpable prostatic tissue) previ-

TABLE 2. EFFECT OF TESTOSTERONE PROPIONATE ON CREATINE RETENTION IN BOYS

Patient, Age	Control Period			After Androgen Injection			
	Creatinine	Creatine[1]	C.R.T.[2] (excretion)	Amount	Creatinine	Creatine[1]	C.R.T.[2] (excretion)
	mg.	mg.	%	mg.	mg.	mg.	%
G.B., 7 yr.	436	129	77 99	350	472	156	83 100
N.R., 8 yr.	834	577	65 100	450	753	577	100
G.F., 9 yr.	505	214	61 91	425	539	357	93 100
A.G., 9 yr.	838	83	62 67	300	889	83	27 33
S.B., 10 yr.	794	113	61 90	350	868	80	71 80
L.T., 11 yr.	877	130	36 38	325	849	115	34 42
A.P., 14 yr.	646	194	68 —	585	794	179	69 100
J.K., 15 yr.	1012	322	84 94	300	1001	456	83 100

[1] As creatine.
[2] Creatine retention test.

[3] Chorionic gonadotropin (Follutein) supplied by E. R. Squibb & Sons, New Brunswick, N. J.
[4] Testosterone propionate (Perandren) supplied by Ciba Pharmaceutical Products, Inc., Summit, N. J.

ous to androgen therapy. This boy was not given a course of gonadotropin.

Case L. T., who showed an increased retention or retention paralleling that of a normal adult, was a tall asthenic 11-year-old male. The left testicle was normally placed in the scrotum, the right was not palpable in the scrotum or inguinal canal. This boy also presented marked secondary sexual changes before treatment was instituted which were perhaps augmented by androgen therapy.

DISCUSSION

From the results here presented it can be concluded that, in the doses given, the creatinuria of young males cannot be abolished or even decreased by the administration of gonadotropic or androgenic hormones. Normally these cases do not retain a great deal of the ingested creatine, excreting from 50 to 100%. Following injection of chorionic gonadotropin or testosterone propionate, as illustrated, this retention capacity is not enhanced and indeed, may even be less.

In consideration of *case A. G.* where the opposite was found to be true one cannot be sure that the results were not purely a coincidental finding. These changes may have been occurring normally at this time and were perhaps augmented by the hormone therapy.

Explanations of the creatinuria of childhood are many and varied. The ingestion of protein appears to influence elimination of creatine. Yet there is no direct relation between the amount of protein ingested and the amount of creatine excreted. The relationship differs with different children but is fairly constant for a given child, i.e., one child may excrete more creatine than another though its protein-intake be less (16).

It has been suggested that creatine is a product of amino-acid catabolism and a certain amount is necessary for physiological processes. In children with a high protein intake in proportion to body weight more is formed than is needed and the excess is excreted. A slightly different view has been expressed by Hunter (1). "Creatine is the end product in the catabolism of certain precursors in the protein molecule just as urea is of others. If these precursors are present in excess relative to the demands for protein synthesis they will be transformed to creatine and partly excreted."

Creatinine is believed to be a normal nitrogenous end product of muscle metabolism. The amount excreted gradually increases with age and is not related to protein intake.

Nitzescu and Gantzea (17) conclude that creatinuria of childhood is due to the presence of the growth hormone. In their opinion the growth hormone increases creatinuria, diminishes tolerance to administered creatine, and inhibits the effect of the male hormone on creatinuria.

In considering Buhler's conclusion that androgen has no effect in increasing creatine tolerance in childhood, one must remember that only one dose of androgenic factor (proviron) was given and that orally.

The statement of Buadge (11) that "male hormone stops the creatinuria of childhood" is not confirmed by the results found in this work.

Jailer (13) states that "the injection of testosterone propionate causes an abolition of creatinuria in immature monkeys and increases their capacity to retain creatine." Only 2 of the monkeys are stated to be definitely immature with inguinal testes. The estimation of age in these cases is a comparative estimate based on the weight of the animal. Thus the possibility of their being adolescent rather than immature monkeys must be considered. (Jailer, personal communication). Or, as in the case of some human individuals (*case A. G.*, age 9 years) secondary changes may have begun at an earlier age and thus the quoted result obtained.

SUMMARY AND CONCLUSIONS

Immature males excrete creatine and show impaired retention of exogenous creatine.

Injection of gonadotropin as illustrated in this work produces no significant change in creatinuria and does not increase the capacity to retain creatine.

Injection of androgen as illustrated produces no change in creatinuria nor does it increase the capacity to retain creatine.

None of the procedures produced any significant effect on the level of creatinine excretion.

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Effects of Testosterone Propionate and Stilbestrol on the Mammary Gland Postpartum

[Mammary Engorgement]

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THERE HAVE BEEN SEVERAL REPORTS on the value of testosterone propionate and stilbestrol in combating the pain of breast engorgement and in inhibiting lactation following delivery (1–6). The results reported have, in the main, been favorable and if they are confirmed by a sufficient number of investigators, these materials may be safely added to the obstetrician's armamentarium.

The opportunity was presented for observation of some effects of testosterone propionate on the mammary gland and its secretion following delivery. The study was made on 139 patients. Of these, 55 were used as controls and 84 were given testosterone propionate or stilbestrol. There were 15 patients in whom it was necessary to stop lactation; of these, 7 received testosterone propionate by deep hypodermic injections and 8 were given stilbestrol orally. Sixty-nine patients received testosterone propionate.

The procedure employed for combating the pain of breast engorgement in the control group consisted of the application of ice packs with tight binders to the breasts, the limitation of fluids and the use of codeine. For the patients receiving testosterone propionate no additional treatment was given. The oral dosage of testosterone varied from 20 to 30 mg. as compared to the 10 to 15 mg. when given by deep hypodermic injection. At the first subjective sign of engorgement, the initial dose of testosterone propionate was given, 10 mg. orally or 5 mg. by deep hypodermic injection. This was followed in 6 hours by a second and, if pain persisted, a third was given.

The evaluation of pain was made as follows: no pain, slight pain and much pain. This is, of course, entirely subjective and dependent upon the emotional make-up of the patient. However, since pain was the only thing to combat, we considered the patient's complaint as a reliable gauge. We listed those patients as having much pain who would have received codeine, tight binders, ice packs and limitation of fluids, for relief. These were the only patients who received a third dose of testosterone propionate.

Table 1 shows the effect of testosterone propionate on painful engorgement as compared with the control group. Approximately 57% of the patients in the control group had no pain; 44% of those treated with testosterone propionate had pain. About ¼ of the control group had much pain as compared to ⅓ of the treated patients. The time of onset of engorgement for the control group was 61 hours and for the treated group 57 hours post partum.

TABLE 1. RESULTS OF THERAPY WITH TESTOSTERONE PROPIONATE IN CASES OF BREAST ENGORGEMENT

Engorgement Onset	Control Group 55 Patients		Treated group 69 Patients	
Time of:				
Average	61 hours		57 hours	
Shortest	40 hours		30 hours	
Longest	83 hours		97 hours	
	No.	%	No.	%
No pain	31	57	30	44
Slight pain	11	19	17	24
Much pain	13	24	22	32

Table 2 shows the comparison between the control and treated patients regarding the average time of onset of lactation and the average amount of milk obtained. Of the control group, 6% produced milk on the 2nd day and 38% on the 3rd day so that a total of 44% were lactating by the end of the 3rd day. Of the 69 patients receiving testosterone, none had milk by the end of the 2nd day and only 8% were lactating by the end of the 3rd day. By the 5th day all patients of both groups were lactating and the average amount in each group was essentially the same.

Of the 55 patients in the control group, 5 had to

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give up nursing because of lack of milk. However, 3 of these patients had not nursed their previous babies for the same reason. The remaining 2 patients (one primipara and one multipara) make up 4% of the total. Of the 69 patients receiving testosterone propionate, 8, or 11%, had to stop nursing due to insufficient milk. One of this latter group had not nursed her last baby for the same reason; the remaining 7 patients (6 primiparae and 1 multipara) constitute 10% of the group.

There were 15 patients who were given hormone products to prevent and/or discontinue lactation. Of these, 8 patients had stillbirths, 3 refused to nurse the infants, 2 were unmarried women, 1 patient's baby died at 3 months of age and 1 patient developed mastitis on the 10th day post partum. Seven of these patients were given deep hypodermic injections of testosterone propionate. The total dosage ranged from 50 to 100 mg. in 25 mg. doses at 24-hour intervals. Of these 7 patients, 6 received the initial dose at the onset of engorgement. The 7th patient who had nursed her baby for 3 months was given 50 mg. in 2 days; lactation stopped by the 3rd day. Careful and frequent inspection revealed soft and non-lactating breasts in all cases by the end of the 5th day after treatment was instituted.

TABLE 2.

Days Post-partum	Amount of Milk Produced			
	Control, 55 Patients		Treated, 69 Patients	
	Av. amount, oz.	%	Av. amount, oz.	%
2	2.5	6	0	0
3	2.5	44	3	8
4	5	94	4	91
5	7.5	100	7	100
6	9.5		9	
7	11		11	
8	9		11	
9	11		12.5	

The remaining 8 patients of this group were treated with diethyl stilbestrol. Of these, 4 were given a total of 8 to 12 mg. starting on the 2nd day after delivery, a 1 mg. dose being given 3 times daily. They all had soft, non-lactating breasts within 4 days. Three patients were given a total of 4 to 8 mg. each starting on the 2nd day, 1 mg. being given twice daily. These 3 had in addition to the medication the application of tight binders and ice packs to their breasts. In these 3 cases the breasts were soft and non-lactating within 3 days after treatment was started. The remaining patient who had received no treatment developed mastitis on the 10th day post partum. She had been lactating for about 7 days. Therapy consisted of 1 mg. of stilbestrol 3 times daily for 3 days and ice bags to the involved tissue. The breasts were soft and non-lactating by the 3rd day of treatment and the affected area rapidly healed.

In the control group of 55 patients, 4 developed mastitis. Of these, 2 progressed to abscess formation necessitating incision and drainage. There were no complications in the patients receiving testosterone propionate.

DISCUSSION

The action of these hormone products is generally considered to be a suppression of the mammary secretagogue produced by the pituitary gland (7–10). There is no evidence that the use of testosterone propionate or of stilbestrol in small doses for a short time is injurious to the patient. However, there may be temporary suppression of ovarian activity. These hormone products were noted to have no apparent effect on the involution of the uterus, the amount of lochia and the development of afterpains. There were no unpleasant after effects, nor did we note any local reactions in the areas of injection.

From this study testosterone propionate offers no apparent advantage over the routine treatments employed at present for the control of pain in puerperal breast engorgement. If any effect of this product can be noted with the dosage used, it is one of delay of the onset of lactation without a delay or even with an earlier appearance of engorgement. The ultimate effect of testosterone propionate is probably one of permanently inhibiting lactation as is evidenced by a 10% failure in ability to nurse as compared with 4% in the control group. It is presumptuous to make positive statements on so small a series of cases but if these findings are later confirmed, the use of testosterone propionate for such minor puerperal difficulties as painful breast engorgement should be discouraged.

In patients in whom it is advantageous to subdue or discontinue lactation, testosterone propionate and stilbestrol are equally satisfactory. At the present time, the high cost of the former product plus the fact that it is apparently more effective when used by the parenteral route makes stilbestrol appear to be the choice of available single procedures. This compound used with tight binders and ice packs to the breasts bids fair to become an ideal method for the suppression of lactation.

SUMMARY

A study of 124 patients was made to determine value of testosterone propionate in the prevention of the pain of breast engorgement in the puerperium. The results showed this compound to be of little or no value for this purpose and of some disadvantage

since it caused a delay and discontinuance of lactation.

Testosterone and diethylstilbestrol are useful in preventing or discontinuing lactation.

A combination of diethylstilbestrol with tight binders and ice packs appears to be ideal for suppression of lactation.

Our appreciation is extended to Ciba Products Company, Incorporated, Summit, N. J., for their generous supply of Metandren and Perandren. Also the Eli Lilly and Company, Indianapolis, Indiana, for their generous supply of diethylstilbestrol.

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Stilbestrol Monomethyl Ether[1]

Report on Its Clinical Use

[Menopausal Syndrome]

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INVESTIGATIONS, principally by Dodds and his coworkers, have shown that estrogenic activity is not confined to the naturally occurring substances of steroid structure (1). Over a hundred synthetic substances have been shown to be estrogenic in varying degree. Of these materials by far the most important is stilbestrol. The structural relationship of this synthetic compound to the naturally occurring estradiol is apparent on consideration of the two formulae (fig. 1, 2). Although the over-all dimensions and general architecture of the molecules are similar as are their stereo-chemical configuration, there are certain notable differences. Stilbestrol is characterized by its highly unsaturated nature, and by the aliphatic nature of its side chain as contrasted with the cyclic structures in estradiol (*B* and *C* in fig. 2).

The physiological response elicited by the synthetic estrogens in the therapeutic range has been shown to be identical with that of the natural hormones.

Most investigators believe on the basis of experimentation to date that the availability of estrogen to the animal organism, its metabolism, and its excretion are functions in which the liver plays a major rôle. When the natural estrogens are administered by mouth, the greater portion is metabolized by the liver during the process of absorption (3). With stilbestrol and other synthetic estrogens the degree of breakdown, while proportional to the rate of absorption and elimination, is considerably reduced. This difference in metabolism and absorption probably accounts for the greater oral potency of stilbestrol and also for the incidence of gastro-intestinal upset that occurs with stilbestrol therapy.

For clinical use the most desirable estrogen would combine the following characteristics. It should be *a*), non-toxic, *b*), of a high order of estrogenic activity regardless of the mode of administration, *c*), it should have a prolonged effect to obviate the necessity of frequent injections and *d*), should be inexpensive and readily available. The natural estrogens or their derivatives fulfill these requirements except for the disadvantage of being comparatively expensive and much less active by oral administration. Stilbestrol on the other hand although inexpensive and readily available has been found to give rise to undesirable side effects when used in dosage levels capable of producing a fully cornified vaginal smear. Also, stilbestrol, possibly because of its high solubility and ready availability for all organs produces an immediate rather than a prolonged estrogenic effect. Also, the oral effectiveness is well below that of the parenteral effectiveness.

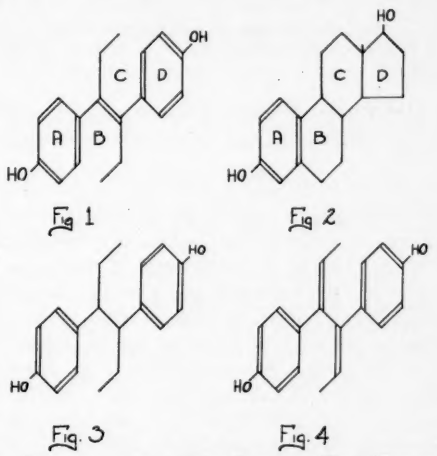

Fig. 1. DIETHYLSTILBESTROL. Fig. 2. ESTRADIOL. Fig. 3. HEXESTROL. Fig. 4. 3,4 BIS P-HYDROXY PHENYL HEXADIENE, 3,4.

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[1] The author is indebted to Dr. Franz C. Schmelkes of the Wallace and Tiernan Products Company, Belleville, New Jersey, for the clinical supply of this material and for furnishing data on the chemical aspects of the compound.

The possibility of suitably modifying the stilbestrol molecule in order to produce the desired physiological effects was therefore investigated. Although a wide variety of modifications of the basic molecular structure of stilbestrol have been reported, as yet no definite correlation between chemical structure and estrogenic activity can be made. Comparatively few changes in the molecule are possible without a decrease in potency. The central double bond may be saturated as in hexesterol (fig. 3), or a second double bond may be introduced as in 3,4 bis p-hydroxy phenyl hexadiene 3,4 (fig. 4) without decreasing the potency.

TABLE 1. ESTROGENIC ACTIVITY OF DI-ALKYL ETHERS OF STILBESTROL

	1 R.U.		
Methyl	25 μg.	Hexyl	30 mg.
Ethyl	50 μg.	Heptyl	750 μg.
Propyl	250 μg.	Octyl	>50 mg.
Butyl	250 μg.	Nonyl	5 mg.
Amyl	600 μg.	Decyl	50 mg.
Hexestrol dimethyl ether	50 μg.		
Hexestrol diamyl ether	600 μg.		

These assay values along with the melting point of the compound have been previously published by Dr. E. E. Reid and Dr. E. Wilson (5).

Variation in the length of the side chains has been reported by Dodds and his collaborators (1) to result in decreased activity. Thus stilbestrol is two or three times as active as the corresponding compound in which 1 of the 2 ethyl groups has been replaced by a methyl group; four to six times as active as the compound in which both ethyl groups have been replaced by methyl groups; and 20 to 30 thousand times as active as the compound where both ethyl groups are replaced by hydrogen. Lengthening of the side chain, as in the compound where both ethyl groups have been replaced by n-propyl groups decreases the potency several hundred times.

It is noteworthy that these compounds in common with other hormones differ in the potency of their stereo and geometric isomers. Stilbestrol, which is supposed to have the *trans* configuration of the substituents about the central bond, seems to be considerably more active than the purest cis isomer thus far prepared.

Dodds and co-workers prepared various esters of stilbestrol with aliphatic acids. They reported that the esters although somewhat less active than the parent compound produced prolonged estrus in rats. Clinical evidence of activity, particularly of the dipropionate ester, indicates that some of the untoward side effects of stilbestrol therapy have been removed, and a prolongation of the period of vaginal cornification achieved.

The observations that methyl ethers of various biologically active materials such as vitamin K, estradiol and estrone may be utilized in the animal organism presumably after demethylation led us to investigate the activity of di-alkyl ethers of stilbestrol. Since we began our investigation Sondern, Sealey and Kartsonis reported the activity of stilbestrol, the dimethyl, the di-ethyl and the di-propyl ethers to be in the ratio of 1:5:10:33. In table 1 we record similar but more extensive data. Although one obtains the desired prolongation of effect with the di-alkyl ethers of stilbestrol, the materials are somewhat too inactive for clinical utilization, and the duration of estrogenic effects is difficult to control.

In an effort to enhance the activity of the di-ethers while still maintaining the prolonged estrogenic effect we have assayed various mono ethers of stilbestrol and hexestrol.[2]

Table 2 shows the assay values obtained. As in the di-ether series, the estrogen value of these derivatives is reduced with increasing chain length.

The mono ethers of hexestrol are significantly less active than those of stilbestrol. This fact presumably arises from the greater ease of demethylation of the stilbestrol mono ethers as compared to the hexestrol mono ether.

The monomethyl ether of stilbestrol was carefully examined. It was found to be almost as active by oral administration as by intramuscular injection, the ratio being 1.25 to 1.0. By mouth it is only slightly less active than stilbestrol and is several times as active as estrone. In fact, its activity by mouth approaches that of estrone by injection. Injections of amounts well above the threshold estrogenic dose result in prolonged estrogenic effects, the prolongation being in proportion to the dose (table 3B).

TABLE 2. ESTROGENIC ACTIVITY OF MONO-ALKYL ETHERS OF STILBESTROL

	1 R.U.		
Methyl	2–2½ μg.	Octyl	50 μg.
Ethyl	5 μg.	Nonyl	84 μg.
Propyl	17.5 μg.	Decyl	200 μg.
Butyl	20 μg.	Undecyl	100 μg.
Amyl	48 μg.		
Hexyl	45 μg.		
Heptyl	50 μg.		
Hexestrol monomethyl ether	8 μg.		
Hexestrol monobutyl ether	50 μg.		
Hexestrol monoamyl ether	150 μg.		

These assay values along with the melting point of the compound have been previously published by Dr. E. E. Reid and Dr. E. Wilson (5).

[2] Some of these derivatives were kindly furnished by Dr. E. E. Reid and Dr. E. Wilson. Others were obtained from the Research Department of the Wallace & Tiernan Products Company.

CLINICAL EVALUATION OF STILBESTROL MONOMETHYL ETHER

The use of estrogens in the menopausal syndrome is a substitutive form of therapy designed to replace absent or diminishing ovarian function. The results of treatment in such cases have become the accepted standard of clinical effectiveness of the various natural and synthetic estrogens. A series of 19 cases with the menopausal syndrome was selected for treatment with the monomethyl ether of stilbestrol. Ten of these were surgical castrates and 9 were patients with senile ovarian changes.

In general, the plan of treatment was to give the hormone by intramuscular injection in sesame oil once weekly for several doses (usually 10 to 15 mg. for a period of 1 month) and then to give a maintenance dose by mouth (usually 1 mg. each night). This regime, however, was varied considerably. In some cases, the patients were maintained on injections for a period of months in order to determine the interval of time that might be permitted to elapse between injections without a return of symptoms. In several patients in which the symptoms appeared within a few weeks following surgical castration, oral therapy only was administered. No untoward reactions were observed with oral therapy. Two patients were nauseated and vomited following parenteral injections of 15 mg., but therapy was resumed without encountering any difficulty at a lower dosage level. In another patient, nausea appeared after the injection of 25 mg.

In general 10 to 15 mg. of monomethyl ether of stilbestrol are sufficient to inhibit the menopausal syndrome (hot flushes, giddiness, throbbing in the head and headache) for a period of 1 week. With doses of 25 mg. by injection, treatment may be spaced as far apart as 3 or 4 weeks. With doses as low as 10 mg. no reactions occur, but occasional nausea is encountered with 15 or 25 mg. dosages. Once the menopausal reactions have been controlled by injections, the patients can usually be maintained on 1 mg. daily by mouth for an indefinite period. In an occasional

TABLE 3A. COMPARATIVE EFFECTIVENESS OF ESTROGENS ORALLY AND PARENTERALLY

		μg. $\simeq$ 1 R.U.
Estrone	By injection	1–2
	By mouth	7.5–15
Stilbestrol	By injection	0.2–0.3
	By mouth	0.6–1.0
Stilbestrol mono methyl ether	By injection	2.0
	By mouth	2.5

TABLE 3B. COMPARISON OF POTENCY OF ESTROGENS AND OF THE DURATION OF THEIR EFFECT WHEN INJECTED[1]

Estrone	
Threshold, 1 to 2 μg.	Prolongation, 10×, 1 to 2 days 25×, 1 to 2 days
Stilbestrol	
Threshold, 0.3 μg.	Prolongation, 10×, 2 days 25×, 2 to 4 days
Monomethyl–Ether of Stilbestrol	
Threshold, 2 μg.	Prolongation, 10×, 5 to 9 days 25×, 10 to 45 days

[1] Prolonged effects have not been obtained by oral administration.

TABLE 4. CASTRATES WITH MENOPAUSAL SYNDROME TREATED WITH MONOMETHYL ETHER OF STILBESTROL

Case, and Age	Indication for Castration	Injection		Subsequent Oral Medication mg./day	Results	Reactions	Number of month Treated
		Dose mg.	Interval wk.				
E.P. 42	Cystic ovaries, endometrial hyperplasia			2	Good	None	3
K.B. 34	Pelvic inflammatory disease	5	1	1	Good	Nausea twice	9
R.C. 41	Myomatous uterus			1	Excellent	None	9
M.S. 32	Lumbar neuroblastoma[1]	25	2	1	Excellent	None	2
G.H. 51	Endometrial hyperplasia	10 25	2 2	1	Excellent	Nausea; once with 25 mg.	10
M.W. 40	Uterine and intraligamentus myoma			1	Excellent	None	9
F.N. 45	Myomatous uterus	10	2	1	Good	Nausea with 15 mg.	3
M.M. 49	Myomatous uterus	10	2		Good	None	3
N.W. 40	Pelvic inflammatory disease			1	Excellent	None	3
H.M. 23	Pelvic inflammatory disease			1, 3×; 1	Good	Some nausea	3

[1] Castration result of repeated irradiation.

case as much as 2 to 5 mg. daily may be required. In mild cases, particularly for symptoms appearing within 2 to 3 weeks after castration, oral medication alone is frequently adequate.

In table 4 and in the case histories the results of therapy are presented in more detail.

Mrs. G. H. The patient, aged 51, has been married for 29 years. She has two children and had two abortions. On June 5, 1940, the uterus, tubes and ovaries were removed because of menorrhagia associated with subserous and intramural fibroids. In November 1940, she complained of hot flushes which came as frequently as every three or four hours. These were accompanied by dizziness and fullness in the head. Ten mg. of monomethyl ether of stilbestrol were injected intramuscularly once weekly. This dose was well tolerated, but there was a tendency for the flushes to return at the end of 5 days. The intramuscular dose was then increased to 15 mg. once weekly with complete control of flushes. This treatment was continued for 2 months. The dose was then increased to 25 mg. which controlled the flushes from 10 to 12 days. There was some nausea with the first dose but not with subsequent doses of 25 mg. At the end of 4 months, the patient was given tablets of monomethyl stilbestrol ether, 1 mg. each. These were taken one every other night, but did not completely control the flushes. Three weeks later, the dose was changed to 1 mg. every night. For the past 5 months, the patient has been doing well on this dosage.

Mrs. M. W. The patient, a married woman, aged 40, had attacks of abdominal pain for 4 years, the pain radiating across the abdomen and sometimes to the back. Most of the tenderness appeared to be low and in the midline. Palpation of the abdomen revealed a mass in the left adnexa. At operation, Aug. 30, 1938, a large intramural myoma and bilateral chocolate cysts of the ovaries were found. The appendix, uterus, tubes and ovaries were removed. The patient did well for one year after the operation; after which there was a return of abdominal distress. Another operation was performed for an intra-ligamentary parovarian cyst on Nov. 27, 1939. Following this, the patient improved and gained in weight. In 1940 she had gained 10 pounds and was free of abdominal distress. In December 1940, however, she was having hot flushes every 2 hours and was feeling nervous and tense. She did not have strength to complete a day's work. She was given 1 mg. of monomethyl ether of stilbestrol daily. Within a period of 2 weeks the patient had regained her normal energy and had lost her nervous, tense feeling. She has since been taking 1 mg. daily and has been free from symptoms in the past 9 months.

Mrs. K. B. The patient is a married woman aged 34 with two children, who had a previous hysterectomy 5 years ago. On Sept. 3, 1940 an exploratory laparotomy was done for adhesions, and both tubes and ovaries were removed. Since that time she has been having continual abdominal distress with nausea and frequent vomiting. She has had attacks of diarrhea and severe headaches and has lost 20 pounds in weight. Before the patient left the hospital in September 1940, she was having flushes and was put on stilbestrol by mouth, 1 mg. every other day. However, within 2 weeks she returned complaining of constant nausea every morning with the spitting up of frothy material and repeated vomiting. Stilbestrol was discontinued and the headaches and flushes soon returned. On Oct. 30, 1940 she was given 15 mg. of monomethyl ether of stilbestrol intramuscularly. The night of the injection she vomited and was nauseated for the next 24 hours. The patient was not treated for 2 weeks, and was then given injections of 5 mg. once weekly which were well tolerated but which did not control the headaches. She was then given 1 mg.-tablets to be taken by mouth one each day. These controlled the headaches and flushes. There was a tendency for fullness and loss of appetite after a period of 3 months, and the patient was put on parenteral administration and the tablets were decreased to one every other day. Early in August, 1941 there was a return of the flushes and headaches. The patient was given 15 mg. by injection in three equal doses of 5 mg. at 4-hour intervals to see if her tolerance had increased. Again there was nausea and vomiting, and the patient was returned to the use of 1 mg.-tablets every day. The results have been satisfactory and there has been no nausea or headache.

Mrs. F. N. The patient, a married woman aged 45, had backache and abdominal pain. A tumor was palpated low in the pelvis. At operation in August 1939, both the uterus and ovaries were removed, but when the posterior peritoneum was incised the pelvic mass proved to be the left kidney. The appendix was removed and nothing further was done. The patient's abdominal complaints were relieved, but in February 1940 nervousness, fatigue and flushes became severe. The flushes occurred as frequently as every 4 hours. She was put on stilbestrol tablets, 1 mg. every other night. At the end of 5 days, there was a feeling of fullness, loss of appetite, and flatulence. She was given injections of estradiol benzoate, 1.6 mg., every week for the remainder of the year. In February 1941, the treatment was changed because the patient complained of a feeling of fatigue and depression during the first 2 days following the injection. An injection of 2 mg. of stilbestrol intramuscularly was tried, but the patient vomited 5 times during the night. She was then put on 1 mg. of estrone parenterally twice weekly. Treatment was continued for several months with control of symptoms. Ten milligrams of estrone were then implanted in the back in the form of three pellets. Again, the patient had a feeling of depression and fatigue for several days followed by 2 or 3 weeks in which the symptoms were controlled. In June 1941, the patient was put on tablets of monomethyl ether of stilbestrol, one every other night. These were well tolerated, but did not completely control the feeling of fatigue and hot flushes.

Mrs. R. M. This patient, aged 49, had a spontaneous menopause. The patient had flushes every one-half to 4 hours. Stilbestrol monomethyl ether tablets, 1 mg. daily, were given for 3 weeks with complete relief of symptoms. After 6 months without treatment, there was recurrence in a mild form and 1 mg. every 2 days for 2 weeks was administered. Thereafter, the medication was given only on the appearance of the flushes, but not more than 1 mg.

daily. The symptoms are controlled on 1 or 2 mg. each month at the present time. She has no untoward symptoms.

Miss E. W. This patient, aged 43, had a spontaneous menopause. The patient had flushes every 2 to 4 hours which required 2 mg. of estrone 3 times weekly for complete relief. She could not take stilbestrol because of nausea. The patient was put on stilbestrol monomethyl ether, 1 mg. daily, with complete relief for 3 months of treatment. She has had no untoward symptoms and is perfectly comfortable. She has not needed any medication for the past 2 months.

In addition to the 19 cases of menopausal syndrome just discussed there were thirty cases with a variety of other conditions which were treated with stilbestrol monomethyl ether. In these cases the drug was administered orally in 1 mg. doses daily and occasionally in larger amounts.

There were 6 cases of hypogonadism, the majority with the girdle type of obesity and loss of energy. With one exception, these patients had scanty menstruation and were between the ages of 16 and 24. The treatment consisted of 1 mg. of stilbestrol monomethyl ether and 3 grains of thyroid daily. The drug was well tolerated and clinically effective as judged by the increased energy and decreased weight. These patients showed a tendency to amenorrhea unless the estrogenic treatment was discontinued at intervals or progesterone injections (5 mg. once weekly) were added.

A group of 14 cases with menstrual disorders, including young girls with dysmenorrhea and women in their late thirties or early forties, with lassitude and depression in the premenstruum, was treated. The cases with dysmenorrhea were given 1 mg. of stilbestrol monomethyl ether daily for 10 days preceding the menstrual period. The majority reported improvement. The patients who were depressed in the premenstruum received 1 mg. either daily or every other day. The majority of these cases noted increased libido and enlargement of their breasts. All tolerated the drug well. None of the patients in this group developed amenorrhea.

Four cases of painful breasts, 2 complicated by adenosis, were treated with 1 mg. tablets daily over a period of 2 months, treatment thereafter being discontinued. All of these patients were improved and noticed an increase in the size of the breasts.

TABLE 5. MENOPAUSAL SYNDROME WITH SENILE OVARIAN CHANGES TREATED WITH MONOMETHYL ETHER OF STILBESTROL

Case and Age	Injection		Subsequent Oral Medication	Results	Reactions	Number of Month Treated
	Dose mg.	Interval days				
Da. 39	25	28	1 mg. every other day	Excellent	None	9
Be. 40	10	7		Excellent	None	3
Ei. 49	15	10		Good	None	2
Pr. 43	15	1	1 mg. daily	Excellent	None	6
Ly. 51	10	7		Good	None	2
R.M. 49			1 mg. daily for 6 mo. Thereafter, 1 mg. every 2 days or for flushes only	Patient finally controlled by about 2 mg. monthly	None	6
E.W. 43	Previously treated estrone, then stilbestrol tried; discontinued because of nausea.		1 mg. daily	Excellent	None	3
E.M. 47	5 3×/wk. Menstrual bleeding when discontinued. 5 mg. 3× weekly then resumed.			Excellent	None	5
E.A. 46	5 3×/wk.		1 mg. daily.	Excellent	None[1]	3

[1] The patient vomited twice, but was a diabetic and when disease controlled with insulin the nausea disappeared.

Stilbestrol monomethyl ether was used in doses of 2.5 mg. daily by mouth along with dicalcium phosphate wafers, vitamin D and a diet rich in calcium and phosphorus to stimulate ossification in 6 cases with bone lesions. The drug was well tolerated and ossification was usually stimulated. In one case of osteogenic sarcoma, the patient had metastasis to the lungs with severe cough and was bedridden. Remarkable improvement occurred and the patient has been symptomatically relieved for 9 months. The affected leg had been previously amputated. In a case of pituitary giantism treated with 5 mg. of the drug daily by mouth, further growth was arrested. This patient developed gynecomastia and complained of loss of appetite. One of the patients with giant cell tumor, treated by curettage, could not take the drug in 2.5 mg. doses because of vomiting.

Toxicity of Stilbestrol Monomethyl Ether

In our experience the toxicity of estrogenic com-

pounds must be based largely upon clinical data, since to date no toxic effects have been found in animal experimentation which would permit a quantitative comparison of the toxicity of the various estrogens. Morrell (2), in tabulation of 64 published papers on the clinical use of stilbestrol in 4,507 cases, lists only three authors (reporting on 304 cases) who found no untoward side reactions with the use of this drug. These reactions included, in the order of their frequency, nausea, vomiting, loss of appetite, abdominal distress, headache, diarrhea, drowsiness, vertigo, palpitation, and skin eruptions. Only during pregnancy and the puerperium are toxic manifestations uniformly absent. Liver function studies, blood morphology, blood chemistry, and studies of the urine revealed no significant findings in the cases reviewed by Morrell. The percentage of untoward side reactions increases with the size of the dose.

TABLE 6. EFFECTIVENESS OF VARIOUS ESTROGENS IN THE PRODUCTION OF MAMMARY CANCER IN SUSCEPTIBLE RATS

Estrogen	Potency[1]	Dosage	Av. Time for Cancer	Rats with Cancer	Total dose	Dosage factor[2]
	μg.	μg./day	days	%	mg.	
Injections, estrogen without prolonged action						
Estrone	1.0	200	203	80	34.8	34.8
Estrone	1.0	100	383	100	32.8	32.8
Estrone	1.0	50	548	75	32.5	32.5
Stilbestrol	0.3	200	104	100	17.8	59.3
Stilbestrol	0.3	100	212	100	18.2	60.8
Estradiol	0.3	100	290	50	25.0	83.3
Injections, estrogen with prolonged action						
Stilbestrol monomethyl ether	2.0	50	212	50	9.5	4.8
Stilbestrol dimethyl ether	25.0	500	233	17	116.5	4.6
Estradiol benzoate	0.6	200	120	67	23.6	39.2
Estradiol benzoate	0.6	100	120	63	11.8	19.6
Estradiol benzoate	0.6	5	120	100	0.6	1.0
Estradiol dipropionate	0.5	100	255	75	21.8	43.6
Estradiol dipropionate	0.5	5	120	40	0.6	1.2
Pellets						
Estrone	1.0	5	273	50	9.6	9.6
Stilbestrol	0.3	5	105	20	10.1	33.6
Estradiol	0.3	3	310	67	8.0	26.6
Estradiol dipropionate	0.5	4	280	67	10.0	20.0

[1] Potency indicates the number of micrograms of crystalline hormone necessary to produce full estrus in 50% of the animals (as measured by the vaginal smear) in the author's colony of white rats.

[2] Dosage factor is obtained by dividing the total number of mg. necessary to produce cancer by the estrogenic potency of the hormone.

When administering stilbestrol compounds for a specific effect such as the control of menopausal symptoms, other physiological effects such as increase in the size of the breasts and pigmentation of the nipples, accentuation of libido and delayed or increased uterine bleeding are observed. The effects on mammary development and on uterine bleeding apparently are slightly more pronounced with stilbestrol compounds than with other estrogens.

The five instances of untoward reactions observed by the author in 49 patients treated with the monomethyl ether of stilbestrol are in general similar to those found when stilbestrol is administered, but occur in a smaller percentage of cases and are practically absent in women when the oral method of administration is used. With oral therapy loss of appetite was observed in one patient receiving 5 mg. daily; in another patient, there was vomiting with 2.5 mg. doses. Both of these were boys aged 16 and 17 in whom the drug was used to promote ossification. Since the oral potency of stilbestrol monomethyl ether is approximately the same as that of stilbestrol, it is our impression that the former drug is definitely better tolerated when given by mouth.

Thus, patients who were unable to take stilbestrol by mouth, were able to take corresponding doses of the monomethyl ether. When intramuscular injections are used, the gastro-intestinal symptoms depend upon the size of the dose. In general, injections of from 10 to 15 mg. in oil which will control menopausal symptoms for 7 to 10 days are well tolerated. With high doses of from 15 to 25 mg. untoward reactions will be observed in some cases, but these are usually confined to the initial dose.

Cancerigenic Effects

The comparative cancerigenic effect of a variety of estrogenic compounds on the mammary gland of the rat is the subject of a separate communication. For the sake of brevity, only the following data are recapitulated here (table 6).

The rapidity with which the mammary cancer appears, the percentage of affected animals, the type of changes preceding the cancer, and the pathologic form of the cancer are affected by increased dosage, physiologic potency, duration of the estrogenic action and the period of administration of the estrogenic compound, but not by its chemical structure. The pre-existing state of the mammary gland, the absence or presence of the gonads or the pituitary, and the age of the animal have also been found to be of importance.

The most commonly overlooked factor in studies of this kind is the strain or species susceptibility of the experimental animal. While the rats on which these experiments were performed belong to a strain in which mammary cancer does not occur spontane-

ously, nevertheless, their susceptibility to estrogenic mammary cancer is definite. In other strains of rats such as those described by Zondek, there was a marked resistance to estrogenic mammary cancer. A similar resistance has been found by us in the experiments performed on the white rabbit and on the rhesus monkey.

When estrogens are given in sufficient doses over a sufficient period to produce mammary cancer, there are also profound changes in the endocrine organs and in accessory sex structures. Marked reduction in weight and various forms of atrophy accompanied by tumor formation occur in the gonads, the anterior pituitary, the thymus and in the adrenals.

Stilbestrol and its ethers are similar in their effects to the natural estrogens when given above physiological levels for prolonged periods. The number of mammary cancers produced and the time of their appearance when stilbestrol monomethyl ether is administered is in proportion to its estrogenic potency and the delayed rate of absorption when considered in relation to the natural estrogens.

Approximately 10 mg. of stilbestrol monomethyl ether are required to produce cancer in 50 per cent of the rats in 212 days. The same amount is required if stilbestrol or estrone is used in the form of pellets to obtain a prolonged action. With the estrone pellets, the cancer appeared within 273 days, and with stilbestrol in 105 days. The estradiol compounds which have a prolonged action such as the benzoate and the dipropionate require far less of the hormone for cancer production. A total dose of 0.6 mg. of estradiol benzoate or estradiol dipropionate will produce cancer in 120 days. These facts are brought out in table 6.

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SUMMARY

A series of di-alkyl ethers of stilbestrol have been assayed on the rat.

A series of mono-alkyl ethers of stilbestrol and hexesterol have also been assayed.

Stilbestrol monomethyl ether has been found to be highly effective and comparatively nontoxic orally and by injection when used for treatment in the menopausal syndrome. The results of the clinical use of this drug in 49 cases are given.

The cancerigenic activity of stilbestrol monomethyl ether has been investigated and compared to that of other natural and synthetic estrogens.

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Clinical Experiences with the Sublingual Administration of Alpha Estradiol

[Vaginal Cornification]

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A NUMBER OF INVESTIGATORS have reported that when estrogens are administered orally a considerable proportion, as much as 90 per cent, is inactivated in the liver. Thus, in order to achieve the same estrogenic effect, ten times more material must be given by mouth than is necessary to achieve the same result by hypodermic injection. This same principle applies to other steroid hormones, except that in some cases the hormone is completely inactivated if given by mouth.

The original work by Anderson, Haymaker and Henderson (1) showed that when the steroid hormone, desoxycorticosterone acetate, was dissolved in a propylene glycol-alcohol solution it could be successfully administered sublingually in the treatment of Addison's disease. A number of investigators have applied this same principle to estrogens, androgens, and other hormones. Salmon and Geist (2) have shown that sublingual administration of alpha estradiol produces a typical cornified vaginal smear. The advantages of a highly active oral estrogen are obvious.

Clinical evaluation of various estrogenic materials must take into consideration the effects of large doses every 5 to 7 days, smaller doses 2 or 3 times weekly and still smaller doses daily.

Shorr (3) has reported: "The wider the interval between doses the less efficient is any total amount of hormone, over any given period, in maintaining the level of estrogenic replacement therapy; and for this reason every assay designed to compare the relative effectiveness of estrogens by different routes should keep this principle in mind. The most accurate comparative assays are carried out by daily administrations."

Following this line of reasoning, it would appear that if the daily doses were divided and given 3 or more times daily, the results should be better than one single large daily dose.

Vaginal smears, which show the various degrees of cornification of the vaginal epithelium, are considered the most accurate clinical tests for determining the estrogenic levels. In this investigation, vaginal smears were the only tests used.

Vaginal smear technique: The vaginal material is collected from the lateral walls of the vagina with a curved spatula, spread thinly on a clean glass slide and dried with compressed air. The slide is then stained for 20 seconds with a 2% aqueous solution of basic fuchsin. Excess stain is removed with tap water and the slide is dried with compressed air. It is then ready to evaluate.

In April, 1941, the first series of 98 menopause types of patients was completed. In this series an effort was made to determine the comparative ratio of absorption of α-estradiol in a solution of propylene glycol-alcohol administered sublingually to intramuscular injections. This material was the crystalline α-estradiol dissolved in the glycol-alcohol solution in a concentration of 0.5 mg. or 6,000 Allen-Doisy R.U. per cc.

There is no question but that the technique of administration is of great importance if the best results are to be obtained. There is an optimum amount of solution that ought to be administered at one time, since, if a large volume of the propylene glycol-alcohol solution is administered at one time it mixes with salivary fluids and is likely to be swallowed. Experience shows that 1/10 cc. is suitable for one dose. If the solution is carefully applied one drop at a time, allowing a lapse of a few seconds between each drop, to the sublingual surface directly onto the visible sublingual veins, the absorption is good. This can easily be done by having the patient touch the roof of her mouth with the tip of the tongue and slightly tilt her head back, applying the first drop near the tip of the tongue at the point where the sublingual veins are first visible, and allowing it to trickle down. The single dose of 1/10 cc. (about 4 drops) should be applied in this manner, drop by drop, alternating the drops, on either side of the frenum. With a little practice in front of a mirror the patient will soon become adept and the solution can be administered without difficulty. A small pocket mirror will suffice when the patient is not at home.

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If there is a tendency for salivary fluids to accumulate after administration of the solution, it is better for the patient to swallow the accumulated fluid a bit at a time rather than to swallow all of the material at one time. The surface tension of this solution is very low, 32 dynes per centimeter; thus, if only a small portion is swallowed it is believed that absorption will take place from the upper portion of the esophagus so that no material will reach the stomach.

This material was given to some patients who had been receiving hypodermic injections every 5 to 7 days. It required 0.20 mg. daily sublingually (1/10 cc. 4 times daily) or 2.0 mg. in 10 days to obtain the results afforded by two injections of 1.666 mg. of estradiol benzoate at 5 day intervals. There was confirmation of Shorr's findings in the fact that those patients who had been receiving daily injections of 0.166 of estradiol benzoate to obtain the desired estrogenic level, obtained equal results with daily doses of 0.20 mg. sublingually. It would seem, therefore, that the most rational comparison is with daily doses of both preparations (or routes of administration).

In a recent series of 41 patients an effort was made to determine the variation of the vaginal cornification over a period of 14 days. This was done because some patients seemed to maintain comfort and a high estrogenic level (as determined by vaginal smears) and others had a mild return of their former symptoms with these dosages. The findings are shown in the table.

RESULTS IN TERMS OF VAGINAL CORNIFICATION, OF 4 DOSES DAILY OF 1/10 CC. (OR 0.05 MG., 600 R.U.) EACH OF α-ESTRADIOL IN PROPYLENE GLYCOL-ALCOHOL SOLUTION ADMINISTERED AS DROPS ON UNDER SURFACE OF TONGUE

Number of Cases	Vag. Smear Before Treatment	Vag. Smear After 48 hr.	Vag. Smear After 96 hr.	Vag. Smear After 14 days
Castrates, no recent therapy				
1	+	+	++	+++
2	++	++	+++	++++
Castrates, who had received intramuscular estrogens				
1	+++	+++	+++	++
3	++++	++++	++++	+++
3	+++++	+++++	+++++	+++++
Menopause types, who had received intramuscular estrogens				
12	++++	++++	++++	+++
3	+++++	+++++	+++++	+++
8	++++	++++	++++	+++++
Hysterectomized patients who had received intramuscular estrogens				
5	++++	++++	++++	+++
3	++++	+++++	+++++	+++++

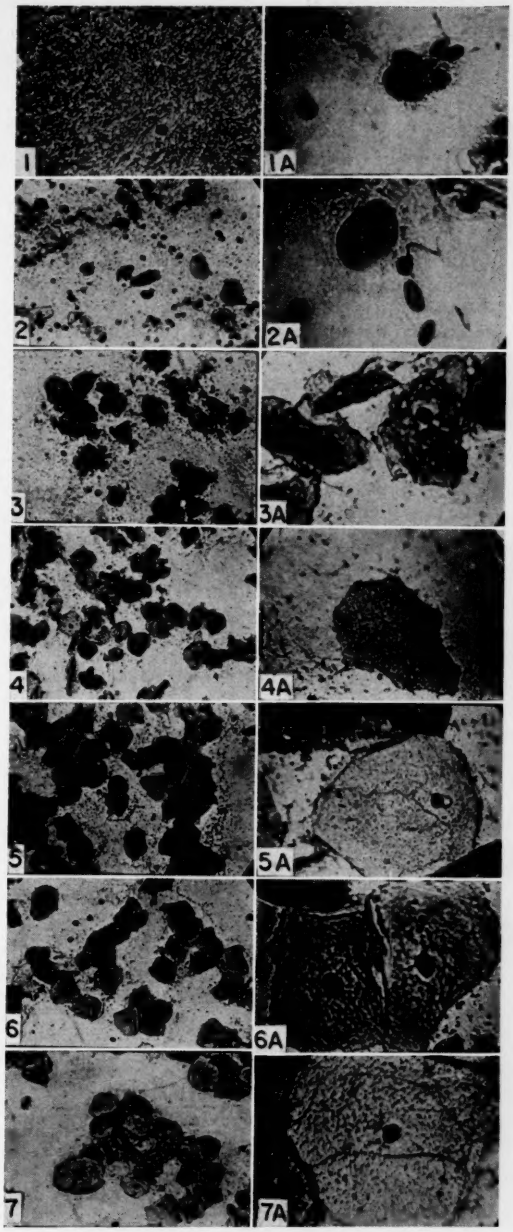

Fig. 1–7 and 1A–7A. PHOTOMICROGRAPHS OF VAGINAL SMEARS low and high magnification. Atrophic smear of artificial menopause in 1. Gradual change up to normal cornification in 5, 6 and 7.

Castrates, who had received no previous therapy, showed improved vaginal cornification at the end of 14 days. Four castrates, who had received recent intramuscular estrogens, showed a slight reduction of

vaginal cornification after 2 weeks of sublingual estradiol, and 3 maintained a high degree of cornification throughout the period of the test.

Fifteen menopause types showed a slight reduction of cornification, whereas 8 patients had smears giving evidence for an improved estrogenic level. Five hysterectomized patients had a slight reduction after 14 days therapy and 3 were definitely improved.

Twenty-four of 41 patients did not maintain quite the same estrogenic level, 3 maintained the original high level and 14 showed much improvement. Those patients who did not quite maintain the required level were given an intramuscular injection of 10,000 R.U. of estradiol benzoate followed by 1/10 cc. of the sublingual estradiol solution 5 times daily (instead of 4) with completely adequate results. Therefore, individualization of dosage is required and effective clinical results are obtainable with this method of administration.

These findings justify the belief that the α-estradiol in propylene glycol-alcohol solutions used sublingually in this investigation produces the same effects on vaginal cornification as the estradiol benzoate administered parenterally.

It will be seen that over a period of 14 days almost comparable results were obtained by the sublingual administration of 2 mg. of α-estradiol when compared with injections of 3.33 mg. during a like period. About one-half of the patients showed a slight regression on the lower sublingual dosage. Undoubtedly, if the same amount of material in milligrams had been given sublingually as given by injection, results would have been exactly comparable.

It may be concluded, therefore, that the sublingual administration of α-estradiol in a propylene glycol-alcohol solution is equally as effective milligram for milligram as α-estradiol benzoate given by hypodermic injection.

I am greatly indebted to Dr. Edward Henderson of the Medical Research Division, Schering Corporation, Bloomfield, New Jersey, for supplying material for these studies.

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Sexual Infantilism of Hypothyroid Origin

[Thyroid and Infantilism]

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For my address as President of The Association for The Study of Internal Secretions in 1928 (1) the title "The Uniglandular Origin of Pluriglandular Diseases" was chosen. In the address was the statement: "The overwhelming majority of endocrinopathies which we are justified in diagnosing exhibit a predominantly uniglandular basis, which anyone properly trained in endocrine diagnosis should be able to recognize. This conception (for which no originality is claimed) is a fundamental and controlling basis for the proper interpretation of endocrine syndromes. An unanalyzed syndrome is a quicksand for therapy. A firm foundation for incretory therapy demands a sharply defined analysis of the symptoms and signs, with emphasis on the gland primarily responsible." A diagnosis of 'pluriglandular dystrophy' or 'multiglandular syndrome' is often merely camouflage for ignorance.

This thesis is abundantly confirmed by such well established endocrinopathies as gigantism, acromegaly, hypophyseal cachexia (Simmonds' disease), hypophyseal infantilism, exophthalmic goiter, myxedema, osteitis fibrosa cystica, tetany, Addison's disease, masculinization due to arrhenoblastoma or an adrenal cortical tumor, sexual precocity due to lesions of the ovary, the testicle, the adrenal cortex or the epiphysis cerebri, eunuchism and hypogonadism, all of which have their primary specific gland focus whose functional derangement causes secondary disturbance in one or more other ductless glands.

In logical sequence therefore "a diagnosis which fixes the responsibility for a clinical complex, ipso facto, like a compass, points the direction by which one should steer one's therapeutic course" (1). A pluriglandular mixture would be sadly futile in the treatment of an amenorrhea due to acromegaly, an arrhenoblastoma of the ovary, or an adrenal cortical tumor, or to anorexia nervosa.

Though the author shares the justified enthusiasm for the newer, remarkably potent synthetic sex hormones, the following case illustrates that these were neither necessary nor primarily indicated in a case of sexual infantilism recognized as due to hypothyroidism.

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The patient, a 27-year-old unmarried woman, was first seen in April 1939, and she was quite uninterested in the opposite sex. She was an only child. Nothing in her past or family history seemed to have any significance. She had always lived close to San Francisco bay.

Her complaints were: shortness of stature (4 ft. 10¾ in.; father and mother were fairly tall); eczema for 10 years; tendency to gain weight easily; and inability to run normally ("legs won't work").

The menarche occurred at 16 years of age, somewhat late, the flow was scanty, and the intervals between periods averaged 5 to 6 weeks but occasionally were lengthened to 2 months. The term 'sexual infantilism' used in the title might be considered an exaggeration, but a glance at her photographs will disclose almost complete absence of secondary sex characteristics (fig. 2, *A* and 3, *A*), there were 2 or 3 hairs on the labia, none on the pubes. There was no axillary hair. Breast development was barely perceptible, little if any mammary tissue being palpable; the nipples and areolae were like a child's. By rectal examination the uterus felt small and the adnexae could not be palpated. In harmony with her severe sexual retardation she had an appearance fully 10 to 15 years younger than her chronological age.

She claimed to have grown normally until 12 years of age when for no apparent reason growth ceased, although she had no accurate records to substantiate this. Her sexual immaturity permitted the prediction that the 'bone-age' would be similarly retarded and such was the case; it was estimated at 14 years when she was 27 years old. The epiphyses of the long bones were incompletely fused with the shafts. All the bones were small and the roentgenograms showed evidence of deficient calcium but without disturbance of bony architecture. The sella turcica was considered to be within normal limits.

The patient admitted a preference for warm weather and a sensitiveness to cold temperatures; she perspired very little. Her temperature was subnormal, 97° F. Her skin and scalp hair were very dry. Two bald spots had developed 8 years before but had responded to scalp treatments which had to be continued regularly. Her arms and legs were entirely de-

void of hair. She had been constipated for many years, constantly requiring cathartics. She was not drowsy in the daytime but slept 9 to 10 hours nightly. She tired easily and had never felt able to work, but she had finished 3 years of college obtaining average grades. Although she was not obviously weak or clumsy, weak leg muscles and stiff knee joints prevented her from running; there was no ataxia. Since 12 years of age, food intake restriction was necessary to prevent obesity. The patient's pulse rate was definitely slow, 58 to 66; her blood pressure 98/70 mm. Hg. The thyroid gland was barely palpable and

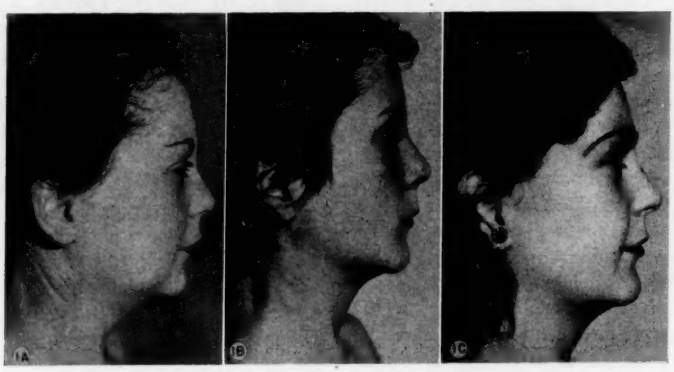

Fig. 1. PROGRESSIVE CHANGES IN APPEARANCE OF 27-YEAR-OLD PATIENT WITH HYPOTHYROIDISM RECEIVING THYROID THERAPY. A, 4/21/39, at outset of treatment; B, 9/25/39, 5 months after beginning thyroid therapy; C, 3/4/41, thyroid continuously and 1 mg. of stilbestrol daily beginning 4/8/40.

certainly was quite small. Careful scrutiny of the features suggested a little puffiness under the eyes which was suspicious of a mild myxedema. The photograph of the patient taken after several months of thyroid therapy, shows a change so startling as to make the original puffiness quite apparent; actually this was barely discernible at first (fig. 1A, B, and C). A B.M.R. of −27% helped to reinforce the clinical impression. Furthermore a certain pallor was corroborated by a hemoglobin value of 50% and a red cell count of 2,960,000. This anemia strengthened the supposition of hypothyroidism. A glucose tolerance curve was rather flat: 73, 89, 123, 78, 79, 80 and 75 mg. per 100 cc. of blood.

In this case there were signs and symptoms pointing to thyroid, anterior pituitary, ovarian and possibly adrenal involvement in a multiglandular confusion. There was shortness of stature without actual dwarfism, markedly retarded ossification, fairly normal weight due to dietary restriction, sensitivity to cold, constipation, bradycardia, hypotension, anemia, low B.M.R., slight puffiness of the face, late onset of scanty and somewhat infrequent menstrual periods, absence of secondary sex characters, and an appearance 10 to 15 years younger than her age of 27 years. Should this case be classified and interpreted as *a*) hypophyseal infantilism, *b*) mild Simmonds' disease, *c*) avitaminosis, *d*) ateliosis, *e*) insuffiance pluriglandulaire, *f*) multiple ductless glandular sclerosis, or *g*) primary hypothyroidism without outright childhood myxedema?

The writer in lectures to medical students and post-graduates, has emphasized the practice of prescribing, wherever possible, one gland extract rather than several, if for no other reason than to be able to judge later on what medication did what. Frequently in complicated or perplexing cases it subsequently becomes necessary to add some other hormone to achieve additional effects if the original hormone failed to supplement completely for the endocrine deficiencies.

Believing that this patient's symptom complex was ascribable primarily to adolescent hypothyroidism, thyroid was prescribed, at first in doses of ½ grain daily of the desiccated substance. Three weeks later this was increased to 1 grain daily. One month after beginning therapy the B.M.R. had risen from −27.3% to −21.7%. By this time greater alertness and animation was noticeable and commented upon by the patient's mother.

Five weeks after commencing treatment unmistakable evidence of beginning breast development was apparent. The puffiness under the eyes had almost disappeared. The patient felt warmer and was much more active. The dose was increased further to 1½ grains daily. Two months after therapy was begun the B.M.R. had reached the normal level of −4.7%.

Three months after instituting thyroid therapy, the dose of the desiccated substance was increased further to 2 grains daily. By this time, and on thyroid

substance alone, the hemoglobin had risen slightly from 50 to 53%, and the red cell count had increased significantly from 2,960,000 to 3,900,000. This specific stimulus to red cell production has been reported previously, notably in a case of masked myxedema with a blood picture simulating pernicious anemia (3).

By the time 4 months had elapsed from the start of treatment the mammary development was most impressive, with firm well formed breasts. The pubic (strictly labial hair growth) remained sparse. No axillary hair had appeared.

Remarkable evidence of the transformation which had occurred, not only in appearance but also in psyche, demeanor and physiological impulses was the admission by the patient, 9 months after beginning treatment, that she feared she might be pregnant—this in contrast to her total lack of interest in the opposite sex 9 months before. She volunteered strong libido and intense gratification. She had planned marrying 2 months later. An Ascheim-Zondek test was negative.

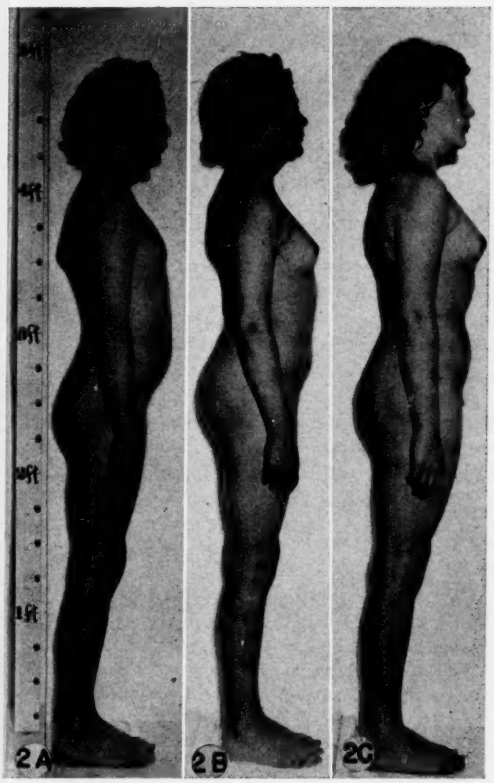

Fig. 2, *A*, 4/21/39, before thyroid therapy; *B*, 2/6/40, 9 months later; *C*, 3/4/41, thyroid continuously and 1 mg. of stilbestrol daily since 4/8/40.

The menstrual intervals, prior to thyroid therapy, had averaged between 5 and 6 weeks, and occasionally were lengthened to 2 months. The period dates since beginning treatment have occurred as follows: 4/10; 5/25; 7/7; 8/2; 8/29; 9/26; 10/22; 11/16; 12/12/39; 1/19/40. It was the delay in the January period following 'exposure' which occasioned the alarm about pregnancy. It is to be noticed that the intervals had been shortened to 25 to 26 days, as a rule.

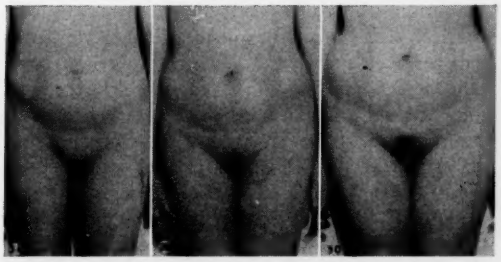

Fig. 3, *A*, 4/21/39, before thyroid therapy; *B*, 2/6/40, 9 months later; *C*, 3/4/41, thyroid continuously; 1 mg. of stilbestrol daily since 4/8/40.

The patient was married in February 1940. Her altered appearance at this time may be observed in figures 1, 2 and 3. She now was an alert, vivacious, pretty, well-developed woman. She had gained 16 pounds, but had grown at 27 years of age only 5/8 of an inch.

In April 1940, after 1 year of treatment consisting solely of thyroid substance, it was reasonable to assume that no further improvement could be anticipated. It was decided to add estrogenic stimulation in the form of stilbestrol, in the hope of inciting greater growth of pubic hair which was still rather scanty. No axillary hair had appeared. Furthermore, though the breasts were well developed, the nipples remained flat and slightly inverted (fig. 2, *A* and *B*). The dose prescribed was 1 mg. daily, orally.[1] In addition she continued to take 2 grains of thyroid substance daily.

Stilbestrol in the enteric tablets form caused no unpleasant side effects, but it is worthy of note that subsequently, on uncoated tablets, the patient became nauseated. This disappeared again when coated tablets were resumed (the dose being the same).

The stilbesterol medication rather promptly provoked protrusion of the nipples, with the usual dark pigmentation of the nipple areolae. More gradually, increased growth of public hair became apparent but even a year later the amount was by no means normal.

[1] The stilbestrol enseals used came from a generous supply furnished by Eli Lilly Co , Indianapolis, Indiana.

(fig. 3, *A*, *B*, *C*). The first axillary hair appeared 8 months after stilbesterol was started and only 3 or 4 short hairs in the right axillae are present after 14 months. Stilbestrol given daily had an unfavorable effect on the regularity of menstruation; the patient was employing contraceptive measures to prevent pregnancy. After several months its administration was confined to 2 weeks between periods; thereafter the periods resumed regularity.

Altogether the patient gained 20 lbs. and for some time has been slightly curtailing her appetite to prevent further gain. She is in excellent health, cheerful, animated and her sexual ardor is thoroughly normal. She continues to take 2 grains of desiccated thyroid daily, and the last B.M.R. (December 1940) was +4.6%. She continues to take stilbestrol, 1 mg. daily for 2 weeks between periods in the hope of obtaining further growth of pubic and axillary hair. In all other respects she seems to have achieved normal adult femininity.

SUMMARY

A case is reported of a 27-year-old unmarried female appearing fully 12 to 15 years younger who had had irregular scanty menstrual periods since 16 years of age, who totally lacked mammary development and axillary hair and who had but 2 or 3 hairs on the labia. She was somewhat below normal height (4 ft. 10¾ in.); her bone age was estimated at 14 years. Slight puffiness of the features, a pulse rate of 58 to 66, a B.M.R. of −27%, marked anemia, preference for warm weather, and easy fatigability suggested adolescent hypothyroidism without outright myxedema.

She was treated for 1 year with thyroid substance alone, the dose being increased gradually from ½ grain to 2 grains daily. This not only elevated her B.M.R. to normal and diminished the anemia, but completely transformed her appearance and demeanor. Her breasts developed promptly, the menstrual periods became regular, personality became vivacious, and, in contrast to a total disinterest in the opposite sex, she married and experienced intense sexual desire and gratification.

At the end of 1 year's treatment, pubic hair remained sparse and no axillary hair had appeared. Stilbestrol (1 mg. daily, orally) was later given which seemed to stimulate additional growth of pubic hair.

The case is reported in order to draw attention to an occasional hypothyroid origin for sexual retardation. Primary deficiency of the anterior pituitary or gonads is not invariably responsible for sexual infantilism.

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Carotinemia in Myxedema Explanation of the Typical Slightly Icteric Tint[1]

[Thyroid and Carotinemia]

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IN PERUSING clinical reports of patients with myxedema, one commonly finds the color of the skin variously described as 'yellow,' 'yellowish,' 'waxy,' or 'wax-like.' Descriptive combinations, such as 'sallow-yellow,' 'yellowish pallor,' and 'slightly icteric,' are used. The pallor is easily explained by the high incidence of anemia in myxedema; but since the anemia is usually of the secondary or microcytic type, the yellowish color in the blood serum is not due to the degeneration products of hemoglobin.[2] In the consecutive cases presented in this paper, the 'yellowish' component invariably has been found to be due to carotinemia.

Interest in carotinemia associated with myxedema was first aroused in 1933 by a patient (*case 1*) with a decidedly yellowish pallor who had most of the internal manifestations of myxedema, including abdominal ascites, but few of the external signs. A marked carotinemia was found which disappeared under treatment with thyroid. The case was reported (3) and the appellation 'internal myxedema' was suggested for similar cases.

All untreated patients with myxedema seen since that time have been tested for carotinemia. In the following small consectuive series it has been present invariably. The test used was that described by Greene and Blackford (4) and Miller (5). The blood serum is mixed with alcohol and petroleum ether. Solubility of the carotin in the petroleum ether is the specific test for its presence in excess of normal.

CASE REPORTS

Case 1, M-72835, previously reported (3). *O. J.*, a woman aged 45, had had internal myxedema for 10 years. She showed all of the internal signs of myxedema including abdominal ascites, but few of the external manifestations. She was in the habit of eating large quantites of vegetables, and frequently carrots. Her skin was described as "pale and slightly icteric." Laboratory investigations showed a secondary anemia, a B.M.R. of −37%, and a plasma cholesterol of 238 mg.%. The serum carotin was 2+ with an icteric index of 15. After 8 days of treatment with thyroid and a carotin-free diet, the test for excessive carotin in the blood serum was negative. Treatment with thyroid was continued but the patient was allowed to take a normal diet. After 2 months the carotin in the serum was 3+; but after 11 months it was again negative. The Rose Bengal liver function test showed improvement after treatment with thyroid. Before treatment the 8-minute specimen showed 62% retention and the 16-minute specimen 44%; after treatment the values were 53% at 8 minutes and 32% at 16 minutes (within normal limits).

Case 2 U-15553. I. S., a woman aged 20, had developed typical childhood myxedema after an operation for 'thyroid cyst' at the age of 7. She entered the hospital because of a spontaneous abortion at 4½ months. Later an ovarian cyst with twisted pedicle was removed. No history of abnormal diet was elicited. Her height was 4 ft. 6 in. Laboratory tests showed a B.M.R. of −25%, and a plasma cholesterol of 303 mg.%. The serum carotin test was positive. The patient did not return for follow-up of endocrine therapy.

Case 3, U-17909. K. B., a woman aged 54, had typical adult spontaneous myxedema of 12 years' duration. No unusual dietary history was obtained. The skin showed a definite pallor. The B.M.R. was −19%; plasma cholesterol, 378 mg.%. The serum carotin test was positive. The patient responded excellently to treatment with desiccated thyroid. One and 3 months after the beginning of treatment, the test for serum carotin was still slightly positive; but after 5 months it was negative.

Case 4, U-40604. T. W., a woman aged 58, had adult spontaneous myxedema of 4 years' duration. The only deviation from the typical clinical picture was that she was somewhat thin. Her B.M.R. was −38%, and plasma cholesterol 953 mg.%. The serum carotin test was positive. She responded well to treatment with thyroid. No further test for serum-carotin was performed.

Case 5, was a patient of Dr. Fred Blake. *L. S.*, a woman 46 years of age, had typical adult spontaneous myxedema with symptoms of 17 years' duration, which had set in after a questionable tuberculous infection following lobar pneumonia. Her skin was described as "pale with a yellowish cast." The B.M.R. was −45%; the plasma cholesterol, 278 mg.%. A mild secondary anemia was

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[1] Aided by a grant from the Christine Breon Fund for Medical Research.
[2] Occasional cases of coexisting myxedema and pernicious anemia have been reported (1, 2).

present. The serum carotin test was positive. She responded well to treatment with thyroid substance. After 3½ months the serum carotin was slightly positive with an icteric index of 7.

Case 6, U-62116. E. S., a woman aged 34, developed symptoms of hypothyroidism after a subtotal thyroidectomy performed 1 year previously. Her skin was described as "pale and ?icteric." The B.M.R. was −37%; the plasma cholesterol, 667 mg.%. The serum carotin test was positive and the icteric index was 15. Before treatment could be instituted, an acute psychosis developed and the patient was transferred to a psychiatric hospital.

Case 7, 29193, was from the clinic group of Dr. Mayo Soley. *V. C.*, a woman aged 49, had post-thyroidectomy hypothyroidism of 5 months' duration. Her B.M.R. before operation had been +42%. At the time of examination, her skin was described as "slightly icteric." The B.M.R. was −13%; the plasma cholesterol, 370 mg.%. The serum carotin test was positive. She responded well to treatment with thyroid.

In addition to these cases, carotinemia was found in a patient with typical Simmonds' disease due to a craniopharyngioma (confirmed by operation). Speculation concerning the relation of the carotinemia to the lowered basal metabolic rate, which was −34% in this case, is interesting. Edwards et al. (6) recently reported that carotene is present in excess in the skin of untreated human male castrates and that it diminishes to normal under treatment with testosterone propionate. A lowered B.M.R. is a frequent finding in male eunuchoidism. It usually rises to normal under treatment with testosterone.

Tests for carotinemia after treatment were carried out in 3 of the 7 cases of our series. In *case 1* the excess carotin rapidly disappeared when treatment with thyroid was combined with a carotin-free diet. However, on resumption of a normal diet, the carotinemia reappeared even though treatment with thyroid was continued. After 11 months of therapy, the blood serum was again free of excessive amounts of carotin. In *case 3* the carotinemia had diminished after 1 and 3 months of treatment with thyroid and had completely disappeared after 5 months, without dietary changes. Also the patient in *case 5* was treated with thyroid alone and showed a diminished intensity of carotinemia after 3½ months.

TABULATION OF CASES

Case, Sex, Age, yr.	Diagnosis, Duration	Remarks on Color of Skin at Examination	B.M.R.	Plasma Cholesterol	Serum Carotin (Icteric Index)		Thyroid Treatment, Duration	Remarks
					Before treatment	After treatment		
			%	Mg. %			Mo.	
1, O.J. ♀, 45	Internal myxedema, 10 yr.	Pale, slightly icteric	−37	238	+ (15)	Negative (8) + Negative	8 days[1] 2 11	Internal myxedema with ascites and secondary anemia. Liver function improved with therapy.
2, I.S. ♀, 20	Childhood myxedema (after surgery when age 7)	None	−25	303	+			Ht. 4 ft., 6 in. Spontaneous abortion at 4½ mo.; ovarian cyst removed later.
3, K.B. ♀, 54	Adult spontaneous myxedema, 12 yr.	Pale	−19	378	+	Weak + Weak + Negative	1 3 5	Typical case; excellent response to thyroid.
4, T.W. ♀, 58	Adult spontaneous myxedema, 4 yr.	None	−38	953	+			Thin type of myxedema; responded well to thyroid.
5, L.S. ♀, 46	Adult spontaneous myxedema 17 yr.	Pale, yellowish cast	−45	278	+	Weak + (7)	3½	Onset after pneumonia and ?tuberculosis.
6, E.S. ♀, 34	Postthyroidectomy hypothyroidism, 1 yr.	Pale, ?icteric	−3	7	+ (15)			Acute psychosis developed
7, V.G. ♀, 49	Postthyroidectomy hypothyroidism, 5 mo.	Slightly icteric	−13	370	+		2½	B.M.R. before operation, +42%.

NOTE: One patient (*case 5*) was seen through the kindness of Dr. Fred Blake. The other patients were from the teaching services of the University of California Hospital and Clinic. One of these (*case 2*) was seen on the Obstetrics and Gynecology Service. The others were seen on the Medical Service. One patient (*case 7*) was from the clinic group of Dr. Mayo Soley.

[1] Carotin free diet during this period.

Interest in carotinemia has been greatly stimulated by the discovery of the relationship of carotene to vitamin A. Stepp and Wendt (7) in 1937 stated that the thyroid hormone is antagonistic to vitamin A and governs the rate of its consumption. In hyperthyroidism the consumption is accelerated and the rate of change from carotin to vitamin A is increased, so that the serum carotin is low. In hypothyroidism the opposite condition is found; the vitamin A in the serum remains normal or low, and the carotin increases. These authors reported corroborative findings in a group of 11 cretins, in all of whom the serum vitamin A was low and the serum carotin was high. This observation would explain the carotinemia in diminished thyroid function whether it be of primary origin as in spontaneous myxedema or secondary to disturbed function of another member of the hormonopoietic system as in Simmonds' disease or eunuchoidism.

Anderson and Soley (8) noted that patients with carotinemia usually show evidence of disease of the thyroid or the liver or of both. They cited the suggestion of Kerr that a primary hepatic injury could prevent the conversion of carotene to vitamin A. In support, Bessey and Wolbach (9) in 1938 stated that circumstantial evidence suggests the liver as the site of formation of vitamin A. Rabinowitch (10) in 1928 reported that the incidence of carotinemia is higher in diabetics than in normal persons. In 1936 Ralli et al. (11), after studying the effects of the administration of carotene in normal persons and in diabetics, concluded that in diabetics the liver shows a comparative inability to change carotene to vitamin A.

It seems logical to assume that a metabolic disturbance rather than an abnormality in diet is responsible for the increased incidence of carotinemia in liver disease, diabetes, and especially in hypothyroidism. In *case 1*, liver function by the Rose Bengal test showed marked improvement after treatment with thyroid (retention before treatment, I, 62%, II, 44%; after treatment, I, 53%, II, 32%; normal, I, 55%, II, 35%). These figures suggest that the liver also is at fault in hypothyroidism. This patient was the only one in this series who had a dietary history of unusually high consumption of carotin-containing foods.

The frequent occurrence of carotinemia would seem to explain adequately the slightly jaundiced appearance that has been noted in many cases of untreated myxedema. These observations await confirmation by other investigators in larger series of cases.

SUMMARY

In 7 consecutive cases of untreated myxedema, coexistent carotinemia was found. It is suggested that this may be part of the typical clinical picture and may explain the 'yellowish' color of the skin so frequently observed. The carotinemia tends to clear gradually under treatment with thyroid substance.

Carotinemia was also noted in a case of Simmonds' disease, and the suggestion is made that it frequently accompanies a low B.M.R. The probable explanation is that the conversion of carotin to vitamin A in the liver is hindered by the depressing effect of the lowered metabolism.

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Diagnosis of Addison's Disease

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[Addison's Disease]

WITHIN RECENT YEARS the older practice of administering desiccated endocrine glands, as a means of substitution therapy in various endocrine disorders, has been replaced largely by the use of specific hormones, hormone-like compounds and related chemotherapeutic agents. With the exception of the thyroid gland, desiccated organs are now known to have little therapeutic value other than a psychologic influence or as a placebo.

Physiologically active endocrine products and synthetic chemical substances are becoming available in rapidly increasing numbers. Their medicinal values, however, are not always adequately established before they are in general use as therapeutic agents. It appears that the therapeutic value of some products is not infrequently overestimated, which may be the result of relying on questionable criteria for determining supposed benefit. In some instances this is obviously due to mistaken diagnosis, whereby alleged benefit of treatment can be explained by an improvement which was not related to the administration of a specific remedy.

In the case of Addison's disease, the foregoing suggestion seems particularly pertinent. During the past 15 years renewed interest in this disease has been stimulated by the development of a more promising type of therapy. The increased number of cases reported in the literature almost suggests a greater incidence of the disease. Because of the relative infrequency of this condition, it seems possible that some cases might have been mistakenly diagnosed. In such cases any therapy may be followed by more striking improvement than usually occurs in well defined Addison's disease and undue confidence in the specific medication employed may result.

The reports in the literature indicate that a diagnosis of Addison's disease is often made on an inadequate clinical basis, and that some genuine cases escape proper diagnosis during the life of the patient. This is not surprising since Addison's disease is not a common ailment. It seems useful, therefore, to record any information which may aid in the recognition and in the treatment of this disease. Experimental investigations on the physiology and pathology of the adrenal glands were begun 25 years ago in collaboration with the late Professor G. N. Stewart, and have led to the study of Addison's disease as a corollary to those researches. In the present summary of these observations, clinical interpretations are based on the results of the experimental as well as clinical investigation.

In uncomplicated cases, diagnosis of Addison's disease usually can be made with reasonable certainty. The classical description of the syndrome, published in 1855 by Thomas Addison (1) includes the combination of symptoms that characterizes the disease. Briefly, this is an association of persistent gastrointestinal disturbances, progressive circulatory and muscular asthenia, and a peculiar discoloration of the skin. If not accounted for otherwise, occurrence of these associated symptoms should suggest Addison's disease.

Usually the disease escapes early recognition and effective treatment, and a subacute exacerbation or an acute crisis develops within a few months from the onset of these symptoms. In untreated cases, or in those in which there is severe and extensive bilateral degeneration of the adrenal cortex, a fatal outcome is inevitable within 1 to 2 years from the period of onset of the related symptoms. Death may occur in consequence of the first acute crisis, more commonly the second and occasionally the third. A notable characteristic of Addison's disease is the occurrence of a more or less abrupt remission during a subacute exacerbation or, not infrequently, from acute crisis.

Most cases of Addison's disease present sufficient criteria for diagnosis. Attempts to precipitate a crisis by depriving the patient of salt or by administering toxic amounts of potassium are too risky if the condition is so far advanced as to suggest the presence of Addison's disease. If a diagnosis of Addison's disease is under consideration and if it is suspected that adrenal cortical degeneration is moderate in extent and is early, then a therapeutic test by administration of interrenalin and saline as a diagnostic aid seems

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justified. The reliability of such a test may be subject to question, yet it is safer than the practice of risking life by the dangerous procedure of inducing an acute crisis in a true case of Addison's disease.

In previous reports (6) certain aids in diagnosis have been presented. These are *a*) aversion to fat in the diet; *b*) the reaction to costo-lumbar pressure; and *c*) changes in the blood comparable with those observed in experimental animals with adrenal cortical insufficiency. Aversion to fats was found, almost invariably, in bilaterally adrenalectomized dogs shortly before the onset of anorexia (7). It is suggested that this may be related to the marked congestion of the pancreas that occurs in these animals. Congestion of the pancreas, has been observed at autopsy in cases of Addison's disease, especially when adrenal degeneration was severe and rapid, and the patient had succumbed in the first acute crisis; inquiry commonly reveals that aversion to fats developed at the time anorexia first became evident. Patients often state that fatty foods induce nausea or diarrhea, whereas prior to the onset of the illness, fats were well tolerated and in some instances were preferred in the diet.

The costo-lumbar pressure reaction, referred to as Rogoff's sign (3), is elicited by moderate pressure with a finger in each costo-lumbar angle. The test is performed with the patient lying flat on the back, completely relaxed. The examiner's hands are placed under the patient so that the index or middle finger rests in the costo-lumbar angle on each side. Moderate pressure is exerted with the fingers, in a forward-inward-upward direction. On the left side the reaction may be obtained more readily if the finger is placed about ½ of an inch below the angle and on the right side well up in the angle. If there is active degeneration of the adrenal gland this procedure elicits a dull pain or aching sensation; usually the discomfort is local. If active inflammation, marked edema, or extensive caseous degeneration of the adrenal is present the sensation is not only local but often is referred toward, but not into, the pelvis of the affected side. These observations have been confirmed by correlating clinical with autopsy findings. Usually, the reaction can be demonstrated easily during acute or sub-acute exacerbations. As repair or regeneration of the adrenal ensues the sign becomes less definite and may finally disappear until another exacerbation occurs.

If the reaction has been present on repeated examinations during a period of some months, and then disappears entirely, while the condition of the patient declines, it can be assumed that the adrenal gland has undergone practically complete degeneration. This has been revealed, repeatedly, at autopsies in cases without gross evidence of associated tuberculosis. Caseous degeneration of the adrenal is commonly associated with clinical evidence of the existence of active or latent tuberculosis elsewhere. Often, calcareous deposits may be detected by roentgenography. These may occur without development of Addison's disease; in such a case the disappearance of the reaction may indicate healing of the gland by calcification, fibrosis, or both.

The clinical significance and value of the costo-lumbar sign is illustrated by the protocols of 2 cases, which follow. In one, a blonde woman without the characteristic skin pigmentation was in acute Addisonian crisis; diagnosis was unquestionably facilitated by relying on this sign. The second case illustrates the advantage of the sign as an index of gradual adrenal damage up to practically complete degeneration.

Case 1, E. H., housewife; 33 years old.[2] Patient was admitted to hospital in acute condition on Aug. 31, 1930. *History.* Family: Father, accidental death, age 58 yr.; mother, 67 yr., stomach trouble; 2 sisters, both sickly. No history of tuberculosis: Personal. Previous health generally fair, except as follows. About 5 years ago became "almost blind" for a while, as the result of the shock of her father's accidental death. Since then, has had frequent headaches; occasional cough. No evidence of cardiac weakness; appetite variable; bowel function irregular, blood in stools once about 5 yr. ago. Nocturia, 1 to 2 times nightly since marriage. Menses always irregular, duration 3–5 days; 1 pregnancy. Male child 5 years old. *Present illness.* For years has complained that feet get cold easily; no tingling sensation. In past 2 months has felt weak, tired easily and has slowly lost weight. Menses ceased 9 months ago; menstruated only once since, last month, 3 days flow. Last winter she had what was diagnosed as "grippe"; had a cold in chest and slight cough, no blood. For the past 6 weeks she had been repeatedly "excited and frightened" over some domestic troubles.

Five weeks ago, ate some green apples which caused epigastric pain, no diarrhea or vomiting but some nausea, no fever. Since then she has felt very weak, fatigue and loss of weight have been progressive. Edema of ankles occasionally during past 2 years. *Physical examination.* Patient is somewhat emaciated. Excitable during examination. Head, eyes, nose, ears, normal. Mucosa of mouth, cheeks and tongue, pale. Thyroid barely palpable. Chest findings normal. Heart sounds weak, regular, rhythmical, no murmurs. Abdomen had slight tenderness in epigastrium and about the umbilicus. Genitalia and pelvis normal. A provisional diagnosis of pernicious anemia? Cancer? was made by the House Staff.

9/1/30: very weak and nervous. 9/2/30: condition unchanged; nauseated. 9/3/30: nausea and cramps in stomach; cyanotic; pulse cannot be felt; extremely weak; B.P. 60/40; hypotension unexplained. B.P. 60–65/20; suggests diagnosis of early Addison's disease, or hemorrhage into

[2] Courtesy of Staff, Cleveland City Hospital, Cleveland, Ohio. Abstract of hospital record.

adrenals. 9/4/30: roentgenogram shows evidence of old (fibrous) tuberculosis scar in apex of left lung. E.K.G., normal mechanism; inverted T leads 2 and 3. Icteric index 10. Temperature chart normal. 9/5/30: patient pulseless, could not get blood pressure. Administered 0.5 cc. of adrenalin in saline, intravenously; followed by blanching of mucus membranes, nausea and dyspnea. 9/6/30: saline-glucose (5%) administered; introduced 3 minims adrenalin via needle in rubber tube and patient had same reaction as mentioned above; no more adrenalin employed.

Consultation note (J.M.R.). History and clinical condition do not support diagnosis of cancer. Pernicious anemia ruled out by blood examination. Roentgenogram of chest shows latent tuberculosis. Two small areas of pigment in mucosa of right cheek and a small one in right angle of lips.

The patient is blonde, therefore, absence of skin pigmentation is not significant. Rogoff's sign present on both sides but decidedly more marked on right side. This would indicate bilateral adrenal degeneration, with more extensive or more recent degeneration of the right gland.

a) The clinical condition of the patient, *b*), history of latent tuberculosis, confirmed by X-ray plate of chest, *c*), presence of costo-lumbar pressure sign, *d*), low blood-pressure (acute crisis), *e*), marked asthenia, *f*), gastro-intestinal disturbance, *g*), moderate decrease in blood sugar and *h*), increase in N.P.N. with moderate increase in urea N, support the diagnosis of Addison's disease. Prognosis very grave; repeated intravenous saline-dextrose and interrenalin was recommended although it appeared unlikely that patient could survive beyond a week.

9/10/30: patient somewhat improved; ate meal with fair appetite. 9/11/30: declining; irrational; pulse imperceptible. 9/12/30: patient died, midnight. 9/13/30: Autopsy, 10 A.M., complete except for brain and cord.

Abstract of notes. Adrenals: The glands could not be identified until the vena cava was opened, the orifices of the adrenal veins identified and a probe was passed up into the veins and left in situ. The kidneys and surrounding tissues, up to the diaphragm and for about the same distance below the kidneys, were then removed, en masse, including corresponding portions of the aorta and vena cava. Carefully dissecting away adjacent fat, the atrophic remains of the adernals were found. Both glands presented only the fibrous capsule containing a little bluish debris in which was seen a small yellowish streak about 1 to 2 mm. thick and about 8 mm. long in the left and less in the right. The bluish debris was more marked in the right. Adrenal veins patent.

Microscopical description. In both organs, the parenchyma, including the medulla, was replaced by edematous, loose areolar tissue containing numerous scattered foci and few localized areas of small round cells resembling lymphocytes. There were large areas of free hemorrhage beneath capsule. Scattered clumps or rows of 2 to 5 cells in syncitial-like arrangement with amphophilic cytoplasm and small round nuclei represented degenerated cortical cells.

Pathological diagnosis: Addison's disease with severe atrophy of adrenal glands, bilateral; fibroid tuberculosis, left upper lobe; congested pancreas; hypertrophied lymphoid tissues, intestines.

Case 2, L. G., housewife, 28 years old.[3] 11/26/27. Patient seen in consultation with Dr. Pearce, at Akron Clinic. *History.* Family. Father, mother, 2 brothers, 3 sisters, all living and well. Personal. Married 2 years, no children; no miscarriages. Whooping cough, measles and scarlet fever in childhood. Menses began at 15 to 16 yr.; generally regular up to present; flow scanty, fair for one day and slight for nearly a week. About a year ago, contracted tonsillitis which confined her to bed for about 2 weeks, this was associated with severe backache; has never felt well since this illness. Developed persistent fatigue. A few months later, in the spring of 1927 she noticed pigmentation of skin on face and hands; fatigue on slight exertion; nausea and vomiting developed. Gradual loss of weight since then. *Present illness.* Patient complains of nausea and frequent bilious vomiting, lassitude and increasing muscular weakness; increasing pigmentation and backache; appetite fair but has aversion to certain articles of diet, especially fats; no cough or night sweats although these had been present formerly. *Physical examination.* Patient uniformly pigmented with accentuation in areas normally pigmented; pigmentation over joints, and surfaces on which pressure of garments is common, also in scars. No pigmentation in mucosa of mouth or tongue. No epigastric pain, but tenderness over epigastrium on pressure, which induces nausea. Mass is felt in lower abdomen on the right side extending from the pelvis upward to below umbilicus. Pulse rapid with excitement. Blood pressure 120/90 mm. Hg. at first but as patient overcame excitement due to examination the pressure declined (in 20 minutes) to 96/60 mm. Hg. Later, it declined to about 85 systolic. Costo-lumbar index (Rogoff sign), right ++, left +.

Tonics and adrenalin, had been used and were continued for a while, but without benefit. 3/6/28: Condition poor; gastro-intestinal disturbances; asthenia; blood pressure 78/60; costo-lumbar index, right ++, left ++. Treatment with interrenalin, by mouth, begun. This was continued for nearly 4½ years throughout the period of survival of the patient to 7/22/32. Occasional intravenous injections of saline-dextrose solution were given as required. Within 2 weeks, her condition improved remarkably. Systolic blood pressure rose and was sustained at about 114 mm. Hg. The patient gained in weight and strength, and was able to resume household duties, which she had been forced to give up; also engaged in social and other activities. An interesting observation is that the menstrual flow was more normal since treatment with interrenalin was begun, and that the patient's condition seemed better during the menstrual periods than at any other time.

During the progress of the case, she had 3 or 4 subacute exacerbations requiring increased dosage of interrenalin and more frequent saline-dextrose injections. These exacerbations appeared to be directly related to overactivity up to the point of fatigue, and in one instance resulted from a long automobile trip. In October, 1929, she had an acute crisis in which the blood pressure fell to about 60 mm. Hg. systolic. There was nausea and vomiting (bile); extreme

[3] Courtesy Dr. R. G. Pearce, Akron Clinic, Akron, Ohio. Abstract of record.

asthenia; costo-lumbar index ++ on both sides. Treatment was followed by decided improvement within a week.

The costo-lumbar index was always more easily elicited and yielded a greater response during each exacerbation. As improvement occurred, it became less marked on both sides. It disappeared and returned a number of times on the left side, and finally disappeared entirely. During the last year of her survival the C-L observations were as follows: 6/28/30, right ++, left −; 9/13/30, right +, left −; 3/30/31, right ++, left +; 10/18/31, right ++, left +; 1/29/32, right −, left −; 5/12/32, right +, left −; 7/21/32, right −, left −; Died, 7/22/32.

7/22/32: Autopsy, complete except for brain and cord. (Courtesy of Dr. D. P. Seecof). Abstract of notes: adrenals. Right: In its situation is found an area 2 cm. in diameter, of highly vascularized fatty tissue containing small yellowish-white and purplish-black nodules some of which are as large as 2 mm. in diameter. These nodules within the fat are contained within a roughly triangular region suggesting the outline of the original gland. The measurements of this region are 5 × 5 × 2 mm. in the form of an isosceles triangle in which the 2 mm. represents the base. The vein cannot be identified. At the vena cava the orifice is identified but the lumen is occluded. Left: Is identified as a small, roughly bean-shaped nodule measuring 2 × 1 × .5 cm. Externally it appears to be made up of a purplish-black tissue similar to that described as nodules for the right. In association with this gland, however, the main vein is identified and traced down to its junction with the renal vein over a distance of 2 cm.; until it is lost within the depth of this nodule it appears normal.

Microscopical description: Right (1) Contained within areolar fatty tissue is a small globular mass completely encapsulated. This mass is made up of very large, somewhat irregular cortical cells with heavily staining cytoplasm and irregular bizarre nuclei. The irregularities of the nuclei vary from pyknosis to vesicle formation and ring forms. The cells show no definite architectural arrangement. They are irregularly distributed and separated by thin vascular connective tissue septa. Within the latter are large foci of round cell accumulation. At one pole of this globular cortical mass there is an adherent layer of fibrous tissue, at one place containing a vessel with a well defined lumen. External to the endothelium of this vessel there are collections of round cells. (2) Elongated piece of tissue, the greater portion of which is made up of areolar fatty tissue containing small islands of 'glandular fat.' On one surface of this fatty tissue is the remains of an adrenal composed for the most part of a thickened fibrous capsule and containing in its central portion fairly normal veins. At irregular intervals throughout this structure are small collections of cortical cells alternating with medullary cells, measuring not over 100 μ. The latter appear intact; the former, similar to those in *section 1*, are irregular and show no architectural arrangement. There are foci of round cells scattered throughout the tissue. In this section, tubercle bacilli found. (3). Essentially similar to *section 2* except that the cortical and medullary masses are larger and well preserved. In this section also there is a small nodule of cortical tissue retaining somewhat the normal histological arrangement. In this section the medulla is well preserved; the round cell infiltration more marked. In places the round cells form the only cellular content between the layers of the capsule.

Left: (1) The outline of the section is triangular, suggesting the normal gland. The capsule is thickened, and contains nodules of cortical cells, irregular in size, staining reaction nuclear content and histological arrangement, the entire picture suggesting regenerated and degenerating cortical tissue. In this section there is no medulla. The central veins are in apposition with the cortical cells (2). Globular mass of cortical tissue showing in places the architectural arrangement of the normal gland, a fairly well defined glomerular and fascicular layer. For the most part, however, the cortical cells are irregularly arranged on a thin vascular stroma. Here and there are small foci of large irregular cortical cells with irregular nuclei. Immediately adjacent to this mass is a large blood space lined by a thin fibrous wall adjacent to what appears to be the remains of the normal gland as indicated by the veins. About the latter are a few small medullary masses and collections of round cells. At a distance from the cortical mass is a sympathetic ganglion mass showing no abnormalities. (3) No adrenal tissue recognized. Adjacent to the large renal vein are lymphoid masses showing slight endothelial hyperplasia and congestion. Within the areolar fatty tissue about these structures are small areas of glandular fat.

Pathological diagnosis: Addison's disease with extensive atrophy of adrenals; ('cytotoxic') bilateral. Pigmentation of skin and mucous membranes; lymphoid hyperplasia in colon; pulmonary emphysema, slight; atrophy parenchymatous organs; healed tuberculous focus, hilum of left lung; fibrous thickening of mitral leaflets; peritoneal adhesion, right iliac fossa; lymphorrhagia of pancreas, thyroid, parathyroid, voluntary muscle; focal necrosis of germinal centers of lymphoid follicles.

Pathology. Absence of active or latent tuberculosis in a case of Addison's disease, with progressive degeneration of the adrenals as evidenced by repeated presence and ultimate disappearance of the costo-lumbar sign, suggests existence of the so-called 'schrumpfnebenniere,' or 'cytotoxic atrophy.' I believe that this type of degeneration also is due primarily to tuberculosis rather than to the suggested action of a specific cellular toxin (*Case 2*). Careful search commonly reveals the presence of a Ghon lesion in the lung or sub-pleural region. This may have undergone caseation or, more often, it has healed by calcification, sometimes by ossification. In case 2 (6, case 3, table 1) serial section of the minute remnant of atrophic cortical adrenal tissue found at autopsy revealed the presence of tubercle bacilli. There was no caseation or calcification of the adrenals.

The suggestion can be made that the tubercle bacilli, may not cause caseous degeneration in some cases but might be responsible for liberation of a toxin that destroys the cells of the adrenal cortex. However, if this were true it would have to be assumed that the

organism must be located in the adrenal to produce such a result. Otherwise, tuberculosis outside of the adrenal should be capable of producing the cytotoxin and Addison's disease would be an almost constant sequel of chronic tuberculosis. It seems more probable that presence of the micro-organisms in the adrenal results in pathologic processes that involve the adrenal blood vessels which then become partly or wholly occluded. Such interference with the circulation can lead to local ischemia, anemic infarction and cellular degeneration with resulting atrophy and fibrosis. Adequate collateral circulation may lead to some regeneration which, co-existing with the degenerative process, yields the characteristic pathology found in 'schrumpfnebenniere.'

By subtotal occlusion of the adrenal blood vessels, it has been possible to create subacute and chronic adrenal cortical insufficiency experimentally in animals in which examination of the adrenals at autopsy revealed the typical picture of the adrenal described as cytotoxic atrophy (8). The clinical manifestations and blood changes, as well as the pathologic appearance of the adrenal glands in these animals were similar or identical with observations in comparable human cases of Addison's disease. The blood changes that occur in experimental animals with subacute or chronic adrenal cortical insufficiency, are similar to but less marked than those which occur in experimental acute adrenal insufficiency induced by total adrenalectomy (9).

Blood changes. During acute and subacute exacerbations there is an elevation of the total N.P.N. In a severe crisis the urea N also increases but not enough to account for the rise in total N.P.N. The significant change is reflected in an elevation of the so-called 'undetermined fraction' of the N.P.N. This escapes notice if the common practice is to determine only one of these factors. For example, in *case 20* (6) chemical examination of the blood performed for diagnostic confirmation revealed the level of urea nitrogen as 18 mg.%, which was within the normal range, while the total N.P.N. was found to be 52 mg.%, decidedly above the upper limit of the normal range. Similar instances have been observed, repeatedly. Total blood calcium usually is elevated in subacute and acute stages of adrenal cortical insufficiency.

The blood chlorides are diminished. This has been attributed to excessive excretion through the kidneys. Loeb et al. (5) observed that the diminution of blood chlorides is associated with a loss of sodium from the body, suggesting a regulatory rôle of the adrenal cortex in relation to Na metabolism. There is evidence in support of the retention of K associated with the loss of NaCl from the blood. In view of the generally recognized fact that available microchemical quantitative methods for estimation of K in the blood are unsatisfactory, this will bear more adequate confirmation. It must be remembered, also, that some of the chemical changes in the blood which occur in consequence of the severe disturbances that are associated with an acute crisis may be secondary to those disturbances and not primarily related to Addison's disease.

A number of authors have emphasized hypoglycemia as a constant manifestation in Addison's disease. This view appears to have originated from observations on adrenalectomized animals that survived for only a short period (2). During the period of survival of untreated adrenalectomized dogs, the blood sugar level rarely declined below the lower limit of the normal range, in animals that survived longer, until a moribund condition developed (9). Definite hypoglycemia appears to be associated only with serious complications and not with loss of adrenal function. The same observations apply in the case of human Addison's disease. In severe crisis, when hemoconcentration occurs, blood chemical changes that are usually found may be considerably modified. This is especially true in the moribund state.

Pigmentation. Addison described a characteristic pigmentation of the skin, to which he referred as 'bronzing.' This pigmentation generally can be distinguished from that which occurs in conditions other than Addison's disease. It may be described as a mixture of various shades of tan with slate grey, usually having a dull, dry, 'dirty' appearance. Many writers on Addison's disease have relied on pigmentation of the skin as pathognomonic. In fact, a relatively large proportion of the cases that have been reported within the past decade have little more than the incidence of this symptom to support the diagnosis. Diminished pigmentation often has been reported to follow treatment. Usually this is only apparent and merely indicates improved circulation during the period of better health of the patient. Occasionally, however, a moderate degree of actual reduction in the amount of pigmentation may occur in those patients that respond well to treatment and survive in fairly good condition for a relatively long period.

Although pigment deposit in the skin and mucous membrances occurs in the classical picture of Addison's disease, it is not pathognomonic unless it is associated with the other definite symptoms described previously. It has been pointed out in other publications (6), that Addison's disease not infrequently occurs with little or no pigmentation of the skin, the diagnosis in such cases having been confirmed at autopsy. In negroes, it is often difficult to detect the additional pigmentation of the skin. Pigment deposit may be found in creases of the skin in the palms of the

hands and the soles of the feet. Another location is in the buccal mucous membrane.

In the cases observed, complete or nearly complete absence of skin pigmentation has occurred only in blonde individuals (*case 1*). Furthermore, it was found that such cases are much more resistant to treatment and that they have a more rapidly fatal outcome. As a general rule, prognosis of a fatal outcome within approximately a half year from the onset of definite symptoms of adrenal cortical insufficiency, has proven correct in blondes. Even if treatment is more effective in some cases, it appears that life can not be prolonged for more than about another ½ year. Where autopsy was performed in cases of this type, extensive atrophy with or without associated fibrosis of the adrenals was found. Addison's disease, when due to tuberculous (caseous) degeneration of the adrenals in blonde individuals appears to be more chronic than when it is due to adrenal atrophy, and usually it is associated with pigmentation of the skin.

In the more severe cases of Addison's disease, especially in those associated with atrophic degeneration of the adrenals, small, rounded, freckle-like, ebony-colored spots often appear on the neck, shoulders, arms and forearms, sometimes on the back and chest. Occasionally, they constitute the only evidence of pigmentation. Their presence and progressive increase in number and points of distribution apparently indicates an advanced stage of the disease, since it was observed that most cases terminated fatally within a few months after the appearance of these ebony-colored spots, particularly in decidedly blonde patients.

Differential diagnosis. The principal source of difficulty in differential diagnosis appears to arise from the fact that pigmentation of the skin is the chief, if not the only symptom commonly relied on to determine the diagnosis of Addison's disease. Certain other diseases, associated with pigmentation, have been confused with Addison's disease, such as chronic tuberculosis, melanotic dermatoses, chronic thyroid disease, hemochromatosis or diabète bronzé, neurocirculatory asthenia in persons with dark complexion, and chronic poisoning with certain metals.

It should not be difficult to distinguish between chronic hypothyroidism and Addison's disease, especially in cases reported with a history of surgical removal of the thyroid (4). Reduction of the basal metabolic rate has been relied on, by some observers, as a significant symptom of Addison's disease. While some cases present a slight reduction, others have an elevation of the B.M.R. In acute crisis of Addison's disease the B.M.R. may decline to a level comparable with that which occurs in hypothyroidism, but these two conditions can hardly be confused if the usual criteria for differential diagnosis are observed.

Real difficulty sometimes arises in distinguishing Addison's disease from chronic tuberculosis without adrenal involvement or with minor adrenal degeneration. Muscular and circulatory asthenia, pigmentation of the skin, and gastro-intestinal disturbances often are associated with tuberculosis. Since this disease is the most common etiologic factor in Addison's disease, differential diagnosis may not be easy. In such a case the costo-lumbar sign is of particular value. A positive reaction is elicited, almost invariably, when active and extensive caseous or hyaline degeneration of the adrenal exists. In the presence of tuberculosis elsewhere this would confirm the probability of existence of Addison's disease. Absence of the reaction would suggest that the adrenals are not involved. As previously indicated, however, tuberculous degeneration may occur in part of the adrenal, in the course of generalized tuberculosis, without leading to Addison's disease. Such degeneration when limited in extent may heal by calcification or fibrosis with improvement in the patient's general condition. If this occurs the costo-lumbar sign may be present during adrenal degeneration and absent when degeneration has subsided. In such a case, absence of the usual blood chemical changes at the time when the costo-lumbar sign is present, complete disappearance of the sign later, and improvement of the patient would indicate that diagnosis of tuberculosis rather than Addison's disease is more probably correct.

Roentgenologic evidence of calcareous deposits in the adrenals, in cases of tuberculosis elsewhere, without other definite symptoms of Addison's disease, more commonly indicates healing of a pre-existing degenerative process in the glands rather than the presence of Addison's disease. Of course, recurrence of degeneration and ultimate development of Addison's disease can and undoubtedly does occur in some of these cases, and the patient again yields a positive costo-lumbar sign until complete degeneration (or regeneration) of the gland takes place. However, the mere presence of a calcified area in the adrenal region, revealed by roentgenography in a patient with latent tuberculosis, does not suffice to establish a positive diagnosis of Addison's disease. Such patients may live for years without manifesting any of the unmistakable evidences of serious adrenal cortical insufficiency. Unless other symptoms occur, the diagnosis ought to be limited to tuberculosis, though keeping in mind the possibility of ultimate development of Addison's disease. It may be mentioned that calcified areas are found frequently in the adrenals of normal experimental animals and in glands obtained from the abattoir.

This type of case can explain statements that have been made to the effect that some patients with Adison's disease have survived for many years.

Tuberculosis may exist for years without involving the adrenal glands, though the patient may manifest some of the symptoms that occur in Addison's disease. Finally, extension of the disease to the adrenals may result in the development of Addison's disease and a fatal termination within a few months. Usually, careful study of the case can determine the approximate period when the Addisonian syndrome developed as a complication of the preexisting tuberculosis. In estimating duration of survival in Addison's disease, this period should not be confused with the much earlier period that corresponds with the time of onset of tuberculosis.

While treatment of Addison's disease directed toward relieving the consequences of adrenal cortical insufficiency, mainly by substitution therapy, has resulted in amelioration of symptoms and prolongation of life (10), there is much to be desired in the way of still more effective therapy. Diagnosis of the syndrome rarely is possible until the disease is well advanced and irreparable damage to the adrenal glands has occurred. If earlier diagnosis were possible we could hope for more satisfactory results of treatment or, perhaps, prevention of the disease by guarding the adrenals against influences which lead to degeneration.

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Treatment of Addison's Disease with Interrenalin (Adrenal Cortex Extract)

[Addison's Disease]

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THE FIRST DEMONSTRATION that active endocrine material can be extracted from the adrenal cortex, and that it is capable of prolonging life and mitigating symptoms in completely adrenalectomized animals, was by Rogoff and Stewart (1) in 1925. Their experimental observations constitute the basis for the method that is now generally employed in the treatment of Addison's disease. The first demonstration that substantial benefit may be derived from administration of potent adrenal cortex extract, in Addison's disease, was published by the same authors (2), in 1929. Amelioration of symptoms was the outstanding observation in 7 patients that had been under treatment with interrenalin,[2] in the form of an extract of adrenal cortex, for periods ranging from approximately 6 to 18 months.

Other articles (3), were followed by a second report (4), in 1932, which included 14 additional cases together with further observations on the original 7. It was clearly shown, by comparison with a control group of 12 cases, that substitution therapy with interrenalin not only caused relief of symptoms but prolonged life in a large proportion of the treated cases. Further clinical experience with Addison's disease and continued experimental animal investigations on adrenal insufficiency warrant publication of another report concerning this method of treatment.

During the past 15 years, observations have been made on patients with Addison's disease treated by the method which originated from the investigations on adrenal insufficiency and its correction in experimental animals. This consists of administration of interrenalin, with or without supplementary intravenous injections of physiologic salt solutions. In 1925, it was demonstrated that completely adrenalectomized animals can be kept alive and well for relatively long periods, if potent adrenal cortex extracts, or physiologic salt solutions, are administered (1). Treatment with both resulted in much longer survival, suggesting clinical trial of the same treatment, in Addison's disease.

At present, the most that can be expected from the best available method of treatment in Addison's disease is a substantial prolongation of life with mitigation of the severity, and reduction in the frequency of recurrence of aggravating symptoms. This is obvious from available knowledge of the pathologic anatomy and physiology of the adrenals in this disease, as well as from proper evaluation of the results of treatment. Substitution hormone therapy does not eliminate the underlying cause of adrenal degeneration. Indirectly, by increasing the patient's resistance, this therapy might retard the pernicious influence of the etiologic factor, thus favoring regeneration in the adrenals. However, it cannot wholly remedy that serious factor.

In general, Addison's disease at present must be considered as an incurable and ultimately fatal malady. It is conceivable, though probably hypothetical, that rarely a benign etiologic factor might induce moderate degenerative processes in the adrenals and lead to development of a less severe form of Addison's disease. If such a benign factor were responsive to treatment, or if it subsided spontaneously, adequate substitution therapy might be followed by adrenal regeneration or by cessation of degeneration. This could result in healing of the damaged adrenals, effecting a clinical 'cure.'

Two patients that possibly may be classed among such cases have been observed. However, on strictly scientific premises, it must be admitted that although the clinical diagnosis of Addison's disease was inescapable on the basis of all the determining factors known, there is nevertheless the possibility that the diagnosis could have been an error. This unavoidable conclusion must govern all interpretations that are made regarding the evaluation of any particular therapy.

Formerly, treatment of Addison's disease was based on the assumption that this malady is the result

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[2] Interrenalin is employed as the non-proprietary name for the physiologic, indispensable hormone of the adrenal cortex. Its etymologic derivation is from "interrenal" gland, the name commonly employed by biologists to designate the adrenal cortex tissue. Cortin is a name employed, by various manufacturing firms, for commercial adrenal products.

of functional insufficiency of the adrenal medulla, that is, inadequate epinephrine secretion. That is the basis for the so-called 'Muirhead treatment.' This has been discarded by clinicians generally since it is well established that epinephrine secretion from the adrenals is not essential for life and health (5). The indispensable function of the adrenals is performed by interrenalin, the adrenal cortical hormone. Insufficiency of cortical function is responsible for the serious consequences that occur in Addison's disease. In creating experimental Addison's disease in animals selective degeneration of the cortex commonly occurs while the medulla remains intact (6).

Administration of adrenalin has proven to be of little if any value in Addison's disease. Indeed, it has been observed, frequently, that attempts to elevate the blood pressure by administration of adrenalin, or ephedrin, cause distress and alarming cardiac reactions (7, *case* 1). This is not surprising, since cardiac degeneration with atrophic changes is often revealed at autopsy in Addison's disease. In one instance, the heart weighed only 98 gm. Such a heart can not be expected to sustain a greatly elevated blood pressure without functional embarrassment. Nor is it necessary to assume that 80 to 100 mm. Hg is not adequate blood pressure for functional needs of a patient with Addison's disease, who is otherwise maintained in fairly good condition.

Some clinicians have administered pituitary gland preparations for Addison's disease. The use of desiccated gland, by mouth, scarcely needs comment. It is well known that the pituitary is inactive when given in this manner. Others have thought that an extract of pituitary might be useful, presumably on the assumption that an adrenotropic or interrenalotropic action would be beneficial. Even if it were established that adrenal cortical function is dependent on interrenalotropic pituitary activity, it does not seem probable that adrenals which have undergone and are in active progress of serious, extensive degeneration, could respond adequately to such stimulation of function. There is evidence that the interrelated activity between the adrenals and the pituitary probably is not at all concerned with the indispensable adrenal cortical function (8).

Results of treatment in Addison's disease can be evaluated best if they are related to the known physiology and pathology of the adrenals. Various theories have been proposed to explain the function of these glands, particularly the cortex. Among these are regulation of *a*) electrolyte balance, *b*) water balance, *c*) carbohydrate metabolism and *d*) blood pressure. There is no good reason to accept any one of these individual explanations. Changes occur in all of these factors in various phases of adrenal cortical insufficiency. All of them are included in the entire disturbance. It seems preferable to retain our original view that the adrenal cortex performs an indispensable metabolic function, failure of which is manifested by a severe functional disturbance in which each of these factors participates. The complete picture is one of a profound intoxication following disrupted metabolic regulation.

Accordingly, treatment of Addison's disease is directed toward combating three major factors, *a*) etiologic, *b*) pathologic and *c*) physiologic. In the majority of cases, treatment of the etiologic factor is that of tuberculosis. Insofar as this disease may or may not be responsive, such treatment will determine the progress of the pathologic factor concerning the adrenals. If active degeneration can be retarded, regeneration may be favored by supplying the hormone which the adrenal must elaborate and secrete to sustain life and improve health. The physiologic factor involves not only supplying interrenalin, which the adrenal is incapable of elaborating properly, but also correction of the pathologic physiology that exists in consequence of functional lack of this hormone. Since the symptoms indicate retention of toxic metabolites, dilution and elimination of these may be facilitated by appropriate intravenous administration of physiological liquids.

It was demonstrated (4) that this treatment is capable not only of ameliorating symptoms but that it can effect a decided prolongation of life, if complicating etiologic factors are not rapidly fatal. Some patients were given interrenalin alone, others intravenous injections of salt solutions alone, and most of them received both. Survival for 8 or more years from the time of onset of the disease has occurred in cases where the clinical diagnosis of Addison's disease was beyond question. Two patients, under present treatment with interrenalin, have continued in very satisfactory condition for more than 8 and 4½ years, respectively. Clinical diagnosis in these cases can not be disputed.

Addison's disease was recognized in the first[3] of these cases when an acute crisis followed herniotomy. In the second case, the patient had received a commercial adrenal product (eschatin), parenterally, salt tablets orally, and was on a restricted diet limiting potassium intake for more than a year, without benefit. He was declining rapidly when administration of glycerinated solution of interrenalin alone, by mouth, was begun. This treatment was continued, with marked benefit up to the present. Recently the synthetic drug desoxycorticosterone-acetate was substituted for the adrenal cortex extract that he had been receiving. He suffered a decline in his general

[3] I am indebted to Dr. S. Berger and other members of the staff of Mt. Sinai Hospital, Cleveland, who referred this case to me for observation and treatment.

condition and blood pressure, which improved again when the material was discontinued and interrenalin resumed. At present, he is in excellent condition, has gained in weight, and pigmentation appears decidedly less marked. The following condensed record of the first of these two cases illustrates, strikingly, the beneficial influence of interrenalin in prolonging life and maintaining a fair state of health, in Addison's disease.

Case S. B., laborer; 42 years of age, was admitted to hospital for herniotomy July 25, 1933. Six years ago he had had double herniotomy. Two years ago he was operated for recurrent right hernia. Herniotomy was performed July 26, 1933. The operation led to development of an acute shock-like condition which was distinguishable from surgical shock but not accounted for. On Aug. 2, 1933 consultation (J.M.R) was requested. Patient reported anorexia and gradual loss of weight during the past 2 years; had an aversion to fat in diet; there was nausea but no vomiting. This was associated with pigmentation appearing first in the skin of the face and becoming uniform over neck, shoulders, arms and hands, and particularly accentuated in areas of normal pigmentation. There are pigment patches on the buccal mucosa, tongue, gums and margin of mucosa of lips. Asthenia, compelled to give up his work for past year. Blood pressure 100/60 mm. Hg. B.M.R. +9; blood N.P.N. 41 mg.%, urea N 14 mg.%, sugar 83 mg.%. Another test showed an N.P.N. of 81, urea 15, sugar 86 and NaCl 316 mg.%. Rogoff's sign was positive on both sides, but was more marked on right. Diagnosis, Addison's disease. Intravenous administration of saline-dextrose solution twice daily for few days, then once daily with oral administration of interrenalin was recommended. Decided improvement followed treatment and on Aug. 13, 1933 the blood pressure was 120/88 mm. Hg and the patient was much stronger and up and about. The patient was discharged from the hospital on Aug. 14 and was referred to me for further study and treatment. For more than a year thereafter he required intravenous injections of salt solution at intervals, in addition to oral administration of interrenalin. A number of more or less severe acute exacerbations indicated the need for these injections. Since then he has had no treatment other than interrenalin, except that he favors salty food and fish, and avoids red meats.

In the 8 years that the patient has been under observation, he has maintained a fairly constant weight. The areas of pigmentation in the mucus membrane of mouth and on the tongue are larger than when first observed, and the intensity of color is greater on the exposed parts of the body. Pigmentation at times appears more intense than at other times. This can be related to the general condition, the pigmentation seemingly being intensified when he approaches a sub-acute state and his circulation is less efficient. As he improves, his color appears lighter. Blood pressure is maintained at an average level of about 110/78 mm. Hg. The mental state, which previously was marked by anxiety and worry, has become much less troublesome; he has cooperated admirably, knows the true nature of his ailment, and has repeatedly presented himself, upon request, for demonstration at medical meetings and class lectures.

The practice of administering salt tablets by mouth does not seem desirable. One of the most aggravating symptoms in Addison's disease is gastric irritability, and excessive amounts of salt frequently cause emesis. It is preferable to include a moderate excess of salt in the regular diet, without additional salt medication. Addisonian patients almost invariably crave salt and take adequate amounts in their food. In acute crisis, or in milder subacute exacerbations, intravenous administration of physiologic salt solutions usually prove strikingly beneficial. The additional liquid in the circulation appears to be the chief beneficial agent, since improvement was observed in adrenalectomized animals, when isotonic dextrose solution, without salt, was administered intravenously. It may be that the increased water intake resulting from from oral salt therapy, rather than the salt itself, accounts for much of the improvement that is usually attributed to administration of NaCl in Addison's disease and in experimental adrenal cortical insufficiency.

Often, patients with Addison's disease in an apparently moribund state, like adrenalectomized animals, may be resuscitated from coma by intravenous administration of physiological liquids. The recovery sometimes is quite spectacular, occurring during the injection and before physiologic effects of NaCl would be expected. This can explain some of the striking results that have been reported from the use of certain extracts, especially those of doubtful merit or of admitted impotency, when administered intravenously together with saline solutions. The remarkable symptomatic improvement which results from intravenous administration of fluid, and the potential possibility of spontaneous remission in the course of this disease, sometimes may be misleading when evaluating the effect of substitution therapy.

The therapeutic effect of adrenal cortex extract can not be expected to result as rapidly as, for example, that of epinephrin with its production of hemodynamic effects or insulin with its effects on glycemia. Metabolic effects of thyroid medication are perhaps more comparable. Correction of the severe, complex metabolic disturbances in Addison's disease requires much longer for the physiologic readjustments that must be effected. The very nature of this disease, its etiology and pathology indicate the improbability of a rapid physiologic readjustment.

As a routine procedure in the treatment of Addison's disease, interrenalin is administered in the form of a potent adrenal cortex extract, which has proven to be effective by mouth. At suitable intervals, this has been supplemented by intravenous injections of saline-dextrose solution. Parenteral administration of

interrenalin is useful at times when gastric irritability interferes with oral administration. At such times intravenous saline is essential, and sterile adrenal cortex extract can be included. However, it appears that exacerbations may be prevented, or their frequency and severity minimized, by an occasional series of routine intravenous injections of saline-dextrose solution. This should be done at once if it is observed that the N.P.N. in the blood is increasing.

In all of the observations on treatment of Addison's disease since 1925, the interrenalin employed clinically, by mouth, has been prepared in glycerinated solution, the extract first having been properly tested for potency by its capacity to prolong life in completely adrenalectomized male dogs well beyond the maximum period of survival of untreated control animals. One assay method that has been suggested (9) is based on the capacity of an extract to prevent a rise in N.P.N. or in urea N for a period of 7 to 10 days, in adrenalectomized dogs. Since this is the period of good health in untreated adrenalectomized dogs, when the N usually does not yet increase significantly, the method can not be considered useful.

Potent extracts can be obtained by various modifications of the original process developed between 1917 and 1922, activity of products being demonstrated in 1925 (1). This consists of extraction of adrenal cortex with alcohol or acetone, and purifying by subsequent action of selective solvents, leaving the active interrenalin in aqueous solution. This solution can be concentrated and glycerinated for oral administration, or it can be prepared as a sterile solution for parenteral administration. Combined in tablet form, interrenalin has recently been made available commercially[4] for oral administration. Extraction of these tablets and tests of the extract for potency has demonstrated that the product is capable of prolonging life in adrenalectomized male dogs.

Aside from the therapy already discussed, it is advisable to restrict muscular exertion to exercise sufficient to meet physiologic requirements. Muscular fatigue and nervous tension should be avoided since they often precipitate an exacerbation. Adequate attention to eliminative functions is, of course, necessary. It is well to regulate the diet, limiting the protein intake to minimum requirements and favoring carbohydrate. As already stated, patients crave and take a surplus of salt. If they do not, this should be encouraged. It has not been found necessary to be much concerned about ordinary potassium intake. The amount of potassium in the usual diet of a patient with Addison's disease is not significant. Certainly, if an excess of K, or of any other toxic substance, is part of the diet it can be injurious. The saltpetre in pickled meats, for example, has caused subacute manifestations in one case under my observation.

Synthetic drugs. Desoxycorticosterone acetate, a synthetic drug represented as a product corresponding to the adrenal cortical hormone, has been alleged to produce benefit in the treatment of Addison's disease (10). Administration by subcutaneous implantation of pellets has attracted some attention. It is assumed that this permits slow, gradual, quantitative absorption of the drug, thus avoiding the need for more frequent injections of soluble material. The evidence for this does not appear convincing from a pharmacologic viewpoint. It does not seem a good substitute for quantitative administration when a soluble preparation is available, even if use of the drug were desirable and safe.

Recent reports (11) on the use of this material in Addison's disease indicate that the enthusiasm which marked earlier publications was somewhat premature. The duration of treatment, in cases alleged to have been benefited by the drug, was too short to permit proper evaluation. Supposed benefit in some cases may be explained by the fact that salt, adrenal cortex extract, or both, were also administered during the period of treatment. Furthermore, it will be more convincing if a number of the cases treated with this material will show definite prolongation of life. Confirmation of the diagnosis at autopsy may seem desirable in some cases.

Desoxycorticosterone acetate appears to be not only less, if at all effective in Addison's disease, than potent extract of adrenal cortex, but it has been demonstrated to possess extremely dangerous, toxic properties. The statement (12), that "The treatment of Addison's disease with desoxycorticosterone acetate represents a marked advance in therapy," is associated with striking evidence which proves the very antithesis to that statement. Five cases of Addison's disease were reported. Treatment with desoxycorticosterone acetate was followed in all of them by serious toxic manifestations; among these were pathologic hypertension, cardiac embarrassment and marked edema. In 3 of the cases, actual cardiac failure was caused. The periods of observation under this treatment ranged from 1 to 6 months. Whatever improvement was observed in some of the patients could be attributed to the influence of salt, which all of the patients received or, in some of the cases, to the adrenal cortex extract that was also employed; and it may have been due to the spontaneous improvement that characterizes Addison's disease. While gain in weight is an encouraging clinical observation, this usually favorable circumstance might sometimes be viewed with alarm by the physiologist. In one of

[4] Cortalex, Upjohn Company, Kalamazoo, Michigan.

the cases, the patient showed a gain of 12 pounds in 4 days. This observation, in the light of existing cardiac embarrassment and edema, may be interpreted as an indication of pathologic retention of water, which is reflected in a gain of weight. It appears that the action of desoxycorticosterone acetate does not represent the physiologic rôle of interrenalin; neither is it a satisfactory substitute for properly tested adrenal cortex extract. Its use in Addison's disease can be considered dangerous because of its serious toxic properties (11).

COMMENT

From the foregoing discussion on treatment, there can be little or no doubt about the therapeutic value of properly tested, potent adrenal cortex extract in Addison's disease. Reports in the literature appear confusing as the result of too brief periods of observation, and inadequate criteria for effectiveness of treatment.

As in adrenalectomized animals, the only reliable criterion for determining the efficacy of treatment in Addison's disease is definite prolongation of life. Prior to the introduction of treatment with interrenalin, with or without supplementary administration of salt, the maximum duration of the disease was about 1½ to 2 years. This is revealed from the history of cases, proven at autopsy, and recorded by responsible observers (13). Twelve cases that were observed before the present treatment was developed survived for about the same periods as reported by these authors (4).

Accordingly, evaluation of results of treatment with adrenal extracts, synthetic drugs, or other therapy in Addison's disease of less than 2 years in duration, may be misleading. At most, the results could testify to mitigation of symptoms. In this respect, it should be emphasized that spontaneous remission, sometimes surprisingly abrupt, is a characteristic of Addison's disease. Such a remission might be attributed, mistakenly, to whatever treatment is employed at the time.

Usually, the diagnosis of Addison's disease presents no great difficulty; yet it can not always be made with certainty. There is no one constant, specific or pathognomonic sign by which accurate diagnosis can be assured. At present, absolute certainty of the diagnosis can be established only postmortem. Therefore, to evaluate the potency of adrenal cortex extract, by clinical test in Addison's disease, convincing evidence can be obtained only from those cases that ultimately have come to autopsy. Controversial questions can thus be entirely avoided. The criterion must be as unambiguous as in the case of adrenalectomized animals, and therefore the same, i.e., definite prolongation of life. For convincing evidence, cases treated with adrenal cortex extract should be compared with similar cases not so treated, and total duration of survival determined in both groups.

A previous report (4) included 21 cases of Addison's disease that were treated with interrenalin, and 12 cases that did not receive this treatment. One patient, *case 17* left the city after a year of treatment, markedly improved, and we have been unable to locate him. Six of the remaining patients were still living at the time of publication. Control of two, (*cases 10, 18*) was lost in 1934. Two patients died since the report was published, having survived 1½ and more than 3½ years, respectively, from the time of onset of definite symptoms. In the first of these 2 cases, autopsy revealed bilaterial extensive caseous degeneration of the adrenals, tuberculosis of the lungs and the right knee joint, and miliary tubercles in the liver and kidneys. The other patient had clinical evidence of tuberculosis, but an autopsy was not obtained.

In the cases treated with interrenalin, the duration of survival from the period of onset of the related symptoms ranged between 1 and 7½ years. Diagnosis of Addison's disease was confirmed at autopsy in 10 cases of this group. Of the 12 cases that were not treated with interrenalin the diagnosis was confirmed at autopsy in 7. Total duration of the disease in this group ranged between ½ and 1½ years. Four of the 7 cases had bilateral extensive adrenal atrophy, two caseous and one hyaline degeneration. In the other group, four presented marked atrophy, one extensive atrophy and fibrosis of the left adrenal and practically complete calcification of the remains of the right gland, one granulomatous degeneration, one malignant neoplasm, two caseous degeneration, and one caseous degeneration with calcification.

The number of cases is not large enough to subject to mathematical treatment. However, comparison of the duration of survival of the patients in the treated with the untreated group reveals the longer survival of the interrenalin-treated patients. The average survival period for the treated cases was about 4 times as long as for the cases in the untreated group. Of the 20 patients receiving interrenalin, 8 survived between 1 and 2 years while 12 survived between 2½ and 7½ years.

Limiting the comparison to the cases in which the diagnosis of Addison's disease was confirmed at autopsy, the average duration of survival in the cases that were treated with interrenalin was approximately 3 years (maximum 5½). The average in the group that were treated otherwise was about 0.8 of a year (maximum 1½). The fact that in a significant proportion of the interrenalin-treated cases length of

survival greatly exceeded the maximum survival period of the non-treated cases, is, of course, much more important even than the facts revealed by comparison of averages.

These data constitute a clear and unmistakable demonstration of the beneficial influence of interrenalin, in the treatment of Addison's disease. Mitigation of severity of one or more symptoms alone is not enough to prove effectiveness of treatment. Only decided prolongation of life is a reliable criterion for determining the real value of specific substitution therapy in Addison's disease. The potency of an adrenal cortex extract that is administered should be determined by its capacity to prolong life and good health well beyond the maximum period of survival of suitable control animals, in completely adrenalectomized male dogs.

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Effect of Adrenal Cortical Extract, Desoxycorticosterone, and Added Potassium upon Electrolyte Balance in Normals and in Addison's Disease

[Electrolyte Balance]

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THE DIAGNOSTIC METHODS for adrenal cortical insufficiency are not entirely satisfactory. A reliable one is not available for the diagnosis of mild insufficiencies and those for Addison's disease are not without hazard. The production of a crisis by a high potassium intake either alone or in combination with a low sodium intake is dangerous.

The Wilder (1) method in which a high potassium and low sodium intake are administered for a shorter period is the safest procedure, yet crises continue to develop with this test. It was pointed out in a previous report (2) that patients with Addison's disease are more sensitive to added potassium during periods of sodium chloride depletion than following correction of this depletion. It was also emphasized that sodium chloride restriction can be tolerated for long periods provided the sodium chloride stores are not depleted and provided that the potassium intake is low. Such restriction, however, with the sodium chloride stores depleted may provoke a crisis. These hazards have caused us to consider other possible diagnostic methods.

In a previous study (2) it was noted that adrenal cortical extract did not cause patients with Addison's disease to store sodium at a faster rate provided the sodium intake was high and the potassium intake was low. Hartman (3) and his coworkers, on the other hand, have reported that adrenal cortical extract caused a retention of sodium in normal men. This apparent difference in the reaction of normal men and of patients with Addison's disease to the administration of adrenal cortical extract appeared as a possible diagnostic method which would be free of hazards. The present study was undertaken, therefore, to ascertain the response under identical circumstances of normal persons and of patients with Addison's disease to the administration of *a*) adrenal cortical extract, *b*) of desoxycorticosterone, *c*) of extra potassium, *d*) of adrenal cortical extract administered simultaneously with extra potassium, and *e*) whether or not any differences in response could be of diagnostic value in Addison's disease.

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METHOD

Balance studies were made on sodium, chloride, and potassium in 3 normal subjects and in 3 patients with Addison's disease. All subjects received a Na intake of 12 gm. and a K intake of 2 gm. daily except when extra K was added. The study was made in 3-day periods; a control period usually preceded each experimental period and as a rule, 3 to 5 days elapsed between each series of study. The adrenal cortical extract was administered intravenously on the morning of the first day of the 3-day period in doses from 1,500 to 2,500 dog units; desoxycorticosterone acetate in oil was administered intramuscularly the first morning in 25 mg. doses. The potassium citrate was administered orally in amounts equivalent to 6 gm. of K daily for the period of added potassium intake and also for the period of simultaneous administration of extra potassium and the adrenal cortical extract. The extract was administered intramuscularly daily during this period in doses of from 250 to 750 dog units. In 3 instances a recovery period followed the period of added potassium and extract administration. The daily urinary creatinine and nitrogen were measured in each instance and blood Na and serum K were measured during each period. The methods for analysis were the same as in the previous report (2).

TABLE 1. EFFECT OF ADRENAL CORTICAL EXTRACT ON SODIUM, POTASSIUM AND CHLORIDE BALANCE

Patient No.	Period	Average Daily Sodium Balance gm.	Average Daily Chloride Balance gm.	Average Daily Potassium Balance gm.
	Addison's disease			
1	Control	+5.09	+4.59	+0.57
	After 1500 dog units of adrenal cortical extract	+4.91	+4.58	+0.72
2	Control	+2.51	+1.55	+0.28
	After 2500 dog units of adrenal cortical extract	+2.33	+0.81	+0.37
3	Control	+1.39	+1.16	+0.26
	After 2500 dog units of adrenal cortical extract	−0.13	−0.71	−0.22
	Control	+0.05	−0.33	−0.27
	After 25 mg. desoxycorticosterone	+1.64	+0.91	−0.72
	Normal subjects			
1	Control	+0.06	−1.10	+0.16
	After 2500 dog units of adrenal cortical extract	+1.57	+1.07	+0.37
2	Control	−0.85	−0.82	−0.03
	After 2500 dog units of adrenal cortical extract	+1.01	+1.54	−0.03
3	Control	+0.51	−0.34	+0.34
	After 25 mg. desoxycorticosterone	+1.58	+1.05	+0.11

RESULTS

Effect of adrenal cortical extract and of desoxycorticosterone. It is to be noted from table 1 that the patients with Addison's disease did not store any more sodium following the administration of adrenal cortical extract during periods of high NaCl and low K intake. The normal subjects, on the other hand, did show a retention of sodium even with a high Na intake and there was no apparent initial sodium depletion. A retention of sodium, however, by both the patients and normal subjects was observed following the administration of desoxycorticosterone even though the Na intake was high and there was no Na depletion. The chloride balances followed closely those of sodium and there were no consistent alterations of the K balances. These observations confirm our previous findings that the administration of adrenal cortical extract to patients with Addison's disease does not cause an acceleration of Na storage and they confirm the work of Hartman and coworkers (3) that the extract causes a retention of sodium in normal subjects. Desoxycorticosterone, on the other hand, causes a retention of Na in normal subjects and in the patients.

TABLE 2. EFFECT OF ADDED POTASSIUM ON SODIUM, POTASSIUM AND CHLORIDE BALANCE

Patient No.	Period	Average Daily Sodium Balance gm.	Average Daily Chloride Balance gm.	Average Daily Potassium Balance gm.
	Addison's disease			
1	Control	+4.09	+3.27	−0.41
	6 gm. added K	+4.14	+4.00	+3.80
2	Control	+0.18	−1.45	+0.22
	6 gm. added K	−0.76	−2.62	+3.83
3	Control	+0.71	−0.04	−0.20
	6 gm. added K	−1.57	−2.61	+4.32
	Normal subjects			
1	Control	+0.91	+0.30	+0.26
	6 gm. added K	−0.51	−1.09	+1.64
2	Control	+0.43	+1.15	+0.03
	6 gm. added K	−1.10	−0.53	+1.71

Effect of added potassium. The effect of the administration of potassium to the patients and the normal subjects is shown in table 2. It should be emphasized that there was no Na depletion in *patients 2* and 3, whereas, *patient 1* was still storing sodium. With the addition of potassium the patients stored less Na when the sodium stores were saturated, but it had no effect when the Na stores were partially depleted. The addition of K also caused the normal subjects to

TABLE 3. EFFECT OF POTASSIUM AND ADRENAL CORTICAL EXTRACT ON SODIUM, POTASSIUM AND CHLORIDE BALANCE

Patient No.	Period	Average Daily Sodium Balance gm.	Average Daily Chloride Balance gm.	Average Daily Potassium Balance gm.
	Addison's disease			
2	Control	+0.18	−1.45	+0.22
	6 gm. added K	−0.76	−2.62	+3.83
	6 gm. added K plus 250 dog units of adrenal cortical extract daily	−1.17	−4.07	+1.83
	6 gm. added K plus 750 dog units of adrenal cortical extract daily	−1.76	−9.48	−4.72
	Control	+2.44	+0.29	−2.16
3	Control	+1.97	+2.18	−1.03
	6 gm. added K plus 750 dog units of adrenal cortical extract daily	+1.20	+0.68	+4.98
	Control	+1.30	+1.35	−1.38
	Normal subjects			
1	Control	+0.91	+1.65	−0.18
	6 gm. added K plus 750 dog units of adrenal cortical extract daily	+0.46	−0.55	+2.18
	Control	+2.05	+1.75	−0.24

store less sodium. The chloride metabolism coincided with that of sodium. The patients stored more of the added K than did the normal subjects, and a crisis developed in the first 2 patients, but not in the third.

Effect of added potassium and adrenal cortical extract. The above observations that the normal subject stored less of the added potassium than did the patients indicated that the simultaneous administration of adrenal cortical extract may decrease the storage of K by the patients. It is to be noted from table 3 that such an effect was apparent in *patient* 2, whereas *patient* 3 stored just as much K as in the period without the extract (table 2). It should be noted, however, that *patient* 2 received extra K for 9 successive days. During the first 6 days approximately 17.0 g. of K were stored and during the next 3 days approximately 14.0 gm. were excreted. It is of interest that the patient developed manifestations of mild crisis; namely, weakness, hypotension, abdominal cramps, and diarrhea during the last 3 days when he was in negative K balance. It is possible that the administration of the adrenal cortical extract prevented a more severe crisis and caused the excretion of the potassium. The fact that *patient* 3 stored just as much K with or without the extract casts some doubt upon this explanation. The data are insufficient to draw any conclusions. The administration of adrenal cortical extract apparently lessened, but did not prevent a decrease in Na retention with the addition of potassium. There was apparently no difference in the response to the addition of adrenal cortical extract and the extra K in the normal subject (comparison of tables 2 and 3).

COMMENTS

The response of normal subjects to adrenal cortical extract and desoxycortisterone differs in several respects from that of patients with Addison's disease and the differences may be of diagnostic value. The continued high urinary excretion of sodium chloride during restricted intake is one difference and is well known; it is the basis for the diagnostic method advocated by Wilder and his associates (1). This procedure may be hazardous if the patient's sodium stores are greatly depleted. Our previous study suggests that if this diagnostic procedure is to be employed the hazard of crisis developing may be greatly reduced by correcting to a large extent the existing sodium depletion by a high sodium and low potassium intake for several days prior to the test. The greater urinary excretion of sodium chloride by normal subjects than by patients during a high sodium chloride and low potassium intake as shown in this study may be of diagnostic value. Its value would depend upon a state of Na depletion in the patient with Addison's disease and upon the assumption that the suspected patient did not have sodium depletion. Such a procedure would be relatively free of serious hazards, but depletion of the sodium stores would undoubtedly be encountered in many patients without Addison's disease. Thus the method probably would not be of specific diagnostic significance.

The second difference is the response to added potassium. It has been emphasized by Wilder and his associates (4) that the addition of potassium will provoke a crisis in patients with Addison's disease; they observed a greater urinary excretion of sodium chloride. An induction of a crisis by additional potassium intake has been confirmed (2). It was pointed out in our previous report that patients with Addison's disease were more sensitive to potassium if the sodium stores were greatly depleted than if they were nearer normal. Such a response depends, therefore, upon the sodium stores of the patient. Patients with slight sodium depletion would require larger amounts of potassium, whereas, in patients whose sodium stores were depleted such a dose of potassium would quickly provoke a severe and possibly fatal crisis. The induction of crisis by added potassium entails too great a risk for a routine diagnostic procedure. The greater urinary excretion of sodium chloride by patients following the administration of extra potassium has not been uniform in our studies; normal subjects will also excrete a greater amount of sodium chloride. Patients with Addison's disease will excrete less of the extra potassium than will normal subjects as shown in table 2. This difference in response, however, entails the possibility of provoking a crisis and should not be considered as a diagnostic method.

The third difference between normal subjects and patients is in their response to the administration of adrenal cortical extract and a high sodium and low potassium intake. Our present study indicates a definite difference in the response of patients with Addison's disease to that of normal subjects. If this difference is subsequently confirmed it should be an excellent diagnostic method. There should not be any chance to provoke a crisis. The outstanding difficulty would be the cost of administration of large amounts of adrenal cortical extract. The response apparently depends upon a high sodium chloride intake and possibly a low potassium intake. The cause for this difference in response is not known. Hartman and coworkers (5) have been able to separate the sodium retention factor from the life preserving factor of adrenal cortical extract. It appears, therefore, that the extract employed by us did not contain much of the sodium retention factor, but that there was a sufficient amount of it to cause a sodium retention, provided the adrenal glands of the subject were also secreting some of this factor. That desoxycorticosterone acetate contains more of the sodium retention

factor is shown by the retention of sodium by the patients and by the normal subjects. The response to administration of desoxycorticosterone acetate would not be of diagnostic value.

Adrenal cortical extract will cause a greater retention of sodium in patients with Addison's disease if the patient has a low sodium and potassium intake as shown in our previous study (2). We have been unable to find comparable studies on normal subjects. The fact that normal individuals will store more sodium with a high sodium chloride intake makes it appear likely that they will also store sodium with a low intake. If this be true this response would not be of diagnostic value. There is not a sufficient difference between the response of normal subjects and of patients with Addison's disease to the simultaneous administration of extra potassium and adrenal cortical extract to be of diagnostic significance. The greater retention of potassium during these periods by the patients than by normal individuals may be significant, but the possibility of induction of a crisis would limit its applicability.

SUMMARY

Normal subjects and patients with Addison's disease have been studied under conditions of high sodium chloride and low potassium intake as a basis for deriving possible diagnostic methods. The response to administration of adrenal cortical extract, desoxycorticosterone acetate, extra potassium, and to simultaneously administered extra potassium and adrenal cortical extract has been ascertained. The various possible diagnostic methods are discussed and it has been suggested that the difference in response of normal subjects to administration of adrenal cortical extract from that of patients with Addison's disease may be the basis of a safe and specific test.

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Preoperative Administration of Desoxycorticosterone Acetate in the Prevention of Surgical Shock[1, 2]

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Perla and his associates (1) recently reported that administration of desoxycorticosterone acetate would protect experimental animals from histamine shock. They found that previous administration of solutions of sodium chloride and desoxycorticosterone acetate was more effective than the use of the latter alone. They further administered sodium chloride and desoxycorticosterone acetate preoperatively to patients who were to undergo major surgical procedures. Using as criteria the clinical condition of the patient and the impression of the attending surgeon they felt that they had demonstrated that such preoperative treatment effectively prevented the occurrence of postoperative shock.

On the basis of these observations Perla and his associates advocated the preoperative administration of desoxycorticosterone acetate in all instances in which surgical shock might be anticipated. Widespread trial of this suggestion apparently has been made, but no convincing confirmation has been forthcoming. Because of the possible importance of any such effect, both in war medicine and in general surgery, it was felt desirable to investigate the problem critically and objectively in human subjects.

Any rationale for the use of adrenal cortical extracts or adrenal cortical steroids (such as synthetic desoxycorticosterone acetate) in the prevention or in the treatment of states of shock must accept at least in part the hypothesis of Selye and his associates (2): that such states are associated with a relatively acute adrenal cortical insufficiency resulting from a sudden unfulfilled need on the part of the tissues for the secretion of the adrenal cortex. Acute adrenal cortical insufficiency has been studied intensively as it occurs in human subjects in the crisis of Addison's disease and in adrenalectomized animals. Characteristic and profound changes in the composition of both the blood and the urine occur in acute adrenal cortical insufficiency and these changes, with the possible exception of hypoglycemia, are counteracted rather rapidly by the administration of desoxycorticosterone acetate. It appeared profitable to look for similar changes in the blood and urine of patients suffering from surgical shock or in patients who had undergone major surgical procedures in the absence of shock, and, if they occurred, to determine whether preoperative treatment with desoxycorticosterone acetate might prevent or abolish them.

The results of observations on 19 women undergoing radical mastectomy for treatment of carcinoma of the breast form the material for this study. This operation was selected for a number of reasons. *a*), It is an extensive surgical procedure which frequently is associated with surgical shock by reason of the extent of the operative trauma, the length of the operation, the fairly extensive loss of blood which occurs, and the deep anesthesia required. *b*), Patients could be selected who were in good health except for the presence of a mass in the breast and who therefore could be regarded as otherwise essentially normal subjects. *c*), Ether is usually the anesthetic of choice at the Mayo Clinic in this procedure. It was felt that for the present study ether was preferable to any other anesthetic agent because its effect on the volume and composition of the blood is such as to favor the production of shock and because ether has been the object of more study than have other anesthetic agents. *d*), The operation is one in which for purposes of study the preoperative and postoperative management can be standardized fairly well. *e*), The abdominal cavity is not involved in the operation; consequently many troublesome and uncontrollable factors affecting metabolism of fluids and electrolytes are avoided.

We are deeply indebted to the members of the Division of Surgery and the Section on Anesthesia

[1] Read before the twenty-fifth annual meeting of the Association for the Study of Internal Secretions, Atlantic City, New Jersey, May 2, 1941.

[2] Abridgment of thesis submitted by Dr. Keating to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of M. S. in Medicine.

for their many suggestions and wholehearted coöperation, without which the study would not have been possible.

METHODS

Ten of the patients in this series were not given any desoxycorticosterone acetate and served as controls. The remaining 9 were given the hormone preoperatively as described later. Both the control and the treated groups were studied in the following manner. Blood for analysis was drawn immediately before the operation; in most cases a specimen was obtained during the evening preceding the operation. Subsequent specimens were obtained during the operation prior to any intravenous medication (if such was given), at the end of the operation, and 1.5 hours, 24 hours and in some cases 48 hours after operation. The samples of blood were drawn into a syringe containing heparin and oil, stirred by means of a glass bead in the syringe, immediately transferred under oil to an hematocrit tube, transported in ice and at once centrifuged in a cold centrifuge (20° F.) at 2,800 r.p.m. for 15 minutes. The plasma then was removed and the remainder centrifuged for a total of 2 hours to complete the hematocrit determination.

The plasma was examined for its specific gravity by a falling drop method, and for its content of chloride, potassium and nitrogen. Nonprotein nitrogen and total nitrogen also were determined and from these figures the total plasma protein was calculated. The methods of analysis employed are referred to elsewhere (3).

All urine passed during the remainder of the operative day was collected, as was the 24-hour specimen for the following day. This was analyzed for its content of chloride and sodium. Careful clinical notes were kept of the patient's course during and after operation. The blood pressure was recorded at intervals of 5 minutes during the operation and hourly (or more frequently when necessary) for 24 hours. An effort was made to form an estimate of the volume of blood lost during the operation by grading it on a basis of 1 to 4. The average blood loss was graded 3, excessive quantities 4 and lesser amounts 1 or 2. Careful record was kept of the time relations between the taking of the blood samples, the duration of administration and the amount of the anesthetic agent, the duration of the operation, the character and amount of intravenous fluids administered, and so forth.

RESULTS

Desoxycorticosterone acetate in sesame oil was administered subcutaneously in a single site. One patient was treated with a modification of the regimen proposed by Perla and associates. The patient was hospitalized for 4 days before the operation and each day she received desoxycorticosterone acetate subcutaneously. On the first 2 days she received 10 gm. of NaCl by mouth. On each of the 2 days preceding the operation she received an intravenous injection of 1,500 cc. of physiologic solution of NaCl; extra salt was not given by mouth. The entire preoperative treatment period was conducted as a 'balance study' to determine as precisely as possible what effect was produced by this method. All food was weighed and its salt content calculated; the water intake was kept high and measured accurately. All urine was analyzed for its content of Cl, Na and K. The patient was weighed accurately each day. Significant retention of both salt and water took place, particularly on the day preceding the operation. The patient withstood operation extremely poorly; she bled profusely, exhibited the typical signs of operative shock and presented a most difficult problem for the anesthetist because of an excessive amount of moisture in the lungs. An underlying cardiac condition was suspected as the cause of some of these difficulties, but the effect of the excessive hydration produced by means of the preoperative treatment could not be ruled out as a factor.

It was thought preferable to see if desoxycorticosterone acetate alone, without the factor of preoperative hydration, would produce changes which might appear of value in preventing shock. Two patients were studied by the subcutaneous administration of 20 mg. of desoxycorticosterone acetate 6 hours prior to operation, no other change being made in the routine preoperative care. This period was selected because in experimental studies it had appeared to be an adequate period for the appearance of the effects of desoxycorticosterone acetate.

When the results of treatment of these two patients were unequivocally negative, it was felt that larger doses might be required. The remaining 6 patients were given 40 mg. of desoxycorticosterone acetate in two doses of 20 mg. each. The first dose was given at 9 P.M. of the day before the operation (12 to 14 hours before operation) to ensure that the maximal effect of the hormone would be present during the operation and a second dose was given 2 to 3 hours before operation to ensure a prolonged effect after operation.

Since the results of all three methods described appeared identical, they are summarized in the tables without particular regard for the dose or the method of administration.

COMMENT

In tables 1 and 2 are summarized some of the clinical data on the two series of patients. The patients in the treated series had an average age of 52.7 years; those in the control series an average age of 50.2 years.

The duration of the operation in the treated group averaged 77 minutes; in the control group 80 minutes. Fortuitously the quality and quantity of intravenous fluids administered in the two groups were also comparable. However, sufficient variation was present in the total intake and urinary excretion of fluids to limit seriously the value of the data obtained from the analysis of the urine.

Genuine shock with all its concomitants cannot be said to have been encountered in any instance in either group. No evidence of hemoconcentration was found; all the shocklike states which occurred were relatively mild and responded to treatment. No fatalities occurred and without exception the patients made reasonably rapid recovery after the operation. This is not surprising when it is considered that in the modern hospital the earliest appearance of any of the signs of shock is the signal for prompt and vigorous treatment. The patients comprising this study were treated exactly as they would have been had no study been in progress.

However, a number of patients exhibited states to which the term 'shock' usually is applied; perhaps 'incipient' or 'early' shock would be more accurate terms. Profound fall of blood pressure, a weak, thready pulse, pallor and sweating were encountered frequently during the operation, usually about the time of the removal of the breast or shortly thereafter. Such symptoms were the indication for the intravenous administration of fluids. This state of operative shock occurred in 6 cases in each series. Treatment consisted in the intravenous injection of physiologic solution of NaCl alone in 7 cases, of physiologic solution of NaCl and blood transfusion in 3 cases and of solution of NaCl and acacia in 2 cases.

TABLE 1. UNTREATED PATIENTS

Case	Age of Patient, years	Duration Operation, minutes	Amount of Bleeding, grade[1]	Shock Symptoms	
				During operation	After operation
1	50	65	2	0	0
2	56	45	2	0	0
3	44	60	3	0	0
4	43	100	2	+	+
5	44	55	3	0	0
6	62	90	3	+	0
7	47	110	3	+	0
8	65	90	3	+	+
9	60	90	1	+	0
10	31	95	3	+	0

[1] Graded on the basis of 1 to 4; 1 indicates minimal, and 4 maximal, bleeding.

A second state which might be called 'threshold' or 'abortive' shock occurred postoperatively in a few instances; after leaving the operating room with a good pulse and normal blood pressure the patient on return to her bed would present the clinical picture of collapse, including slow respiration, feeble pulse, sweating, pallor and a fall in blood pressure, and would be extremely slow in recovering from the effects of the anesthetic. In these cases the patient responded in from 6 to 8 hours with no other treatment than warmth, Trendelenburg position, and the intravenous administration of fluids. Such postoperative shock was encountered in 2 of the 10 control cases and in 2 of the 9 cases in which desoxycorticosterone acetate had been given. In only one instance (*case 4*) was much difficulty encountered in improving the state of the circulation.

TABLE 2. TREATED PATIENTS

Case	Age of Patient, yr.	Treatment		Duration Operation, min.	Amount of Bleeding, grade[1]	Shock Symptoms	
		Total dose, mg.	No. of doses			During operation	After operation
11	41	20	1	68	3	+	+
12	65	20	1	92	3	+	0
13	69	50	5	95	3	+	0
14	57	40	2	85	3	+	+
15	68	40	2	80	1	0	0
16	38	40	2	55	3	+	0
17	39	40	2	55	2	0	0
18	42	40	2	93	3	+	0
19	55	40	2	68	2	0	0

[1] Graded on the basis of 1 to 4; 1 indicates minimal, and 4 maximal, bleeding.

Four of the patients serving as controls and 3 of those treated with desoxycorticosterone acetate did not exhibit either the signs or the symptoms of shock at any time during or after the operation.

Determinations of the hematocrit value (fig. 1), specific gravity of the plasma and total plasma protein (fig. 2) were employed as indexes of hemoconcentration. Significant increase in the concentration of the blood was not encountered in either group of patients irrespective of the condition of the patient. Instead, among all patients, treated and controls alike, there was a progressive fall in the values mentioned during and after the operation but no significant differences could be seen between the two series.

The most remarkable feature of the chemical analyses of blood plasma in these cases was the relative absence of any conspicuous variations. Concentrations of plasma electrolytes never varied in either direction beyond the normal range. Differences were far greater between different patients before operation than any variations which occurred in any individual patient after operation. In the control series the concentrations of chloride (fig. 3) and sodium (fig. 4)

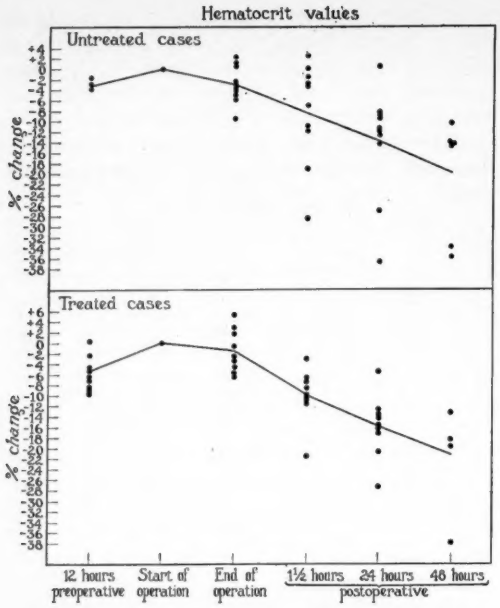

Fig. 1. CHANGES IN HEMATOCRIT VALUES. In this and succeeding figures each determination is expressed as the percentage change from the value of the control specimen obtained immediately preceding induction of anesthesia ('start of operation'). The points representing the average of the values at each interval are connected by the continuous line.

There were no significant differences in the changes of hematocrit in the treated and untreated groups.

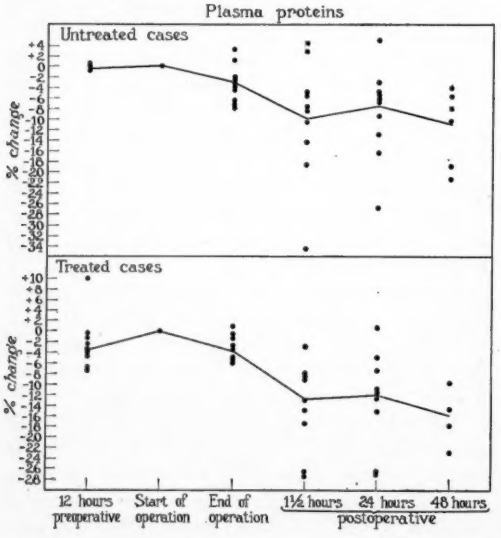

Fig. 2. CHANGES IN PLASMA PROTEINS. As with hematocrit values, determinations of plasma proteins showed a tendency to fall postoperatively. There were no significant differences in changes of plasma proteins in the treated and untreated groups. See legend for figure 1.

in the plasma did not change significantly until the 24-hour sample, when a fall in concentration of the order of 4% was encountered with considerable consistency. Although the decrease was small, the consistency with which it occurred appeared significant. It occurred regardless of the presence or absence of the symptoms of shock and appeared to be unrelated either to the quantity of the salt solution administered or to the amount of electrolytes excreted in the urine. In two cases in which the fall did not occur (*cases 16* and *17*) the 24-hour sample of blood was drawn too soon after an intravenous injection of NaCl for the figures to be of much value.

During the operation the concentration of K (fig. 5)

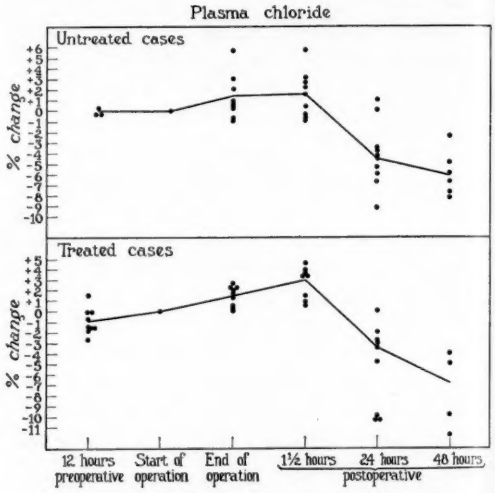

Fig. 3. CHANGES IN PLASMA CHLORIDES. The values obtained for plasma chlorides 1½ hours after operation were in the aggregate slightly higher in the treated than in the untreated series. This difference appears too small to be significant and in all other respects there are no differences between the two groups. See legend for figure 1.

in the plasma in the control cases decreased to 6 to 30% and usually did not fully regain the preoperative level for 24 hours or longer. This decrease has been reported previously and has been attributed to the effect of the anesthetic in depressing the metabolic rate.

The nonprotein nitrogen content (fig. 6) of the plasma in the control series did not change significantly in the specimens obtained during the operation, at its end or one and a half hours later. In the specimens obtained 24 hours after the operation there was a large rise (30 to 80%) in some cases but there was no rise or even a fall in others. When the clinical data were examined with regard to these findings, the cases were found to fall into three groups. Among the pa-

tients who had not received fluids intravenously during operation there was a significant elevation of the N.P.N. content of the plasma at the end of 24 hours. Among the patients who had received intravenous therapy during or immediately after the operation, only those among whom shock symptoms subsequently occurred showed a significant increase in plasma N.P.N. 24 hours after operation. Both these groups also exhibited diminished output of urine during the first 24 hours after operation. Among patients who had received intravenous fluids during operation and did not exhibit symptoms of shock or fall of blood pressure after operation there was a consistent absence of a significant rise in N.P.N. content of the blood. It therefore appears likely that elevation of the nonprotein nitrogen content of the plasma 24

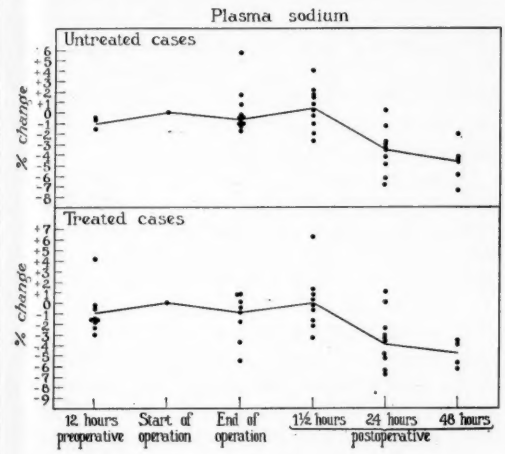

Fig. 4. CHANGES IN PLASMA SODIUM. As in the case of changes in plasma chloride, values for plasma sodium 24 hours after operation averaged 4% less than control values at the start of operation. There were no significant differences between treated and untreated groups. See legend for figure 1.

hours after operation represented transient renal impairment possibly related to an inadequately restored blood volume.

The changes observed in the concentration of Na, Cl and N.P.N. in the plasma were in the direction noted in acute adrenal cortical insufficiency, although they did not occur at the time when symptoms of shock were most likely to be present. The changes in the plasma K and in the concentration of the blood were not in the direction observed in acute adrenal cortical insufficiency. Nevertheless, if these changes could be abolished by the administration of desoxycorticosterone acetate, one might still assume that the former values represented in fact a 'mild' or 'subclinical' degree of adrenal cortical insufficiency resulting from the noxious stimuli of the operation and

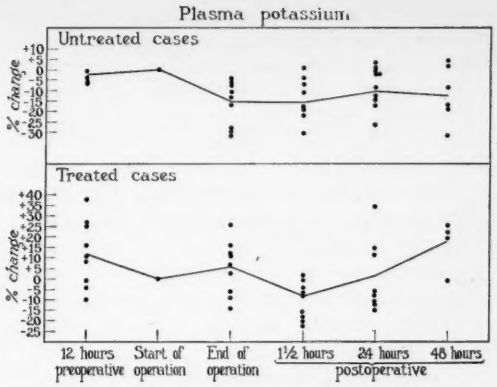

Fig. 5. CHANGES IN PLASMA POTASSIUM. In the untreated group there was a consistent fall in plasma potassium during operation. Preoperative administration of desoxycorticosterone acetate produced in most cases a decided fall in plasma potassium before operation, so that the 'control' determination at the start of operation represents in most instances a subnormal value for potassium. Instead of a further drop of potassium during operation in these cases, there was a rise during operation with a subsequent postoperative fall to values in most instances even lower than the 'control' values. See legend for figure 1.

anesthesia. However, administration of desoxycorticosterone acetate did not abolish these changes. The changes in the blood of the patients in the group treated with desoxycorticosterone acetate were in

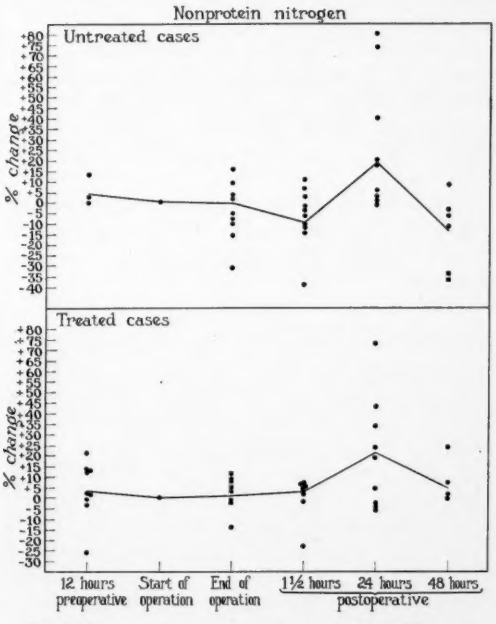

Fig. 6. CHANGES IN PLASMA NONPROTEIN NITROGEN. There were no significant differences in the changes of plasma nonprotein nitrogen in the treated and untreated groups. See legend for figure 1.

most respects identical with those encountered in the patients in the control group and graphs of the two series cannot be distinguished one from the other.

The concentration of K in the plasma was the only determination whose behavior appeared different in the treated and the untreated group. In the blood sample obtained just prior to the operation and after the administration of desoxycorticosterone acetate there was in nearly every instance a rather conspicuous fall in the plasma content of K to levels which were less than or at the lower limit of the normal range, as compared with the normal values obtained the night before the operation. In the first patient, treated with the Perla regimen, a preoperative K level of 12.9 mg. per 100 cc. of plasma was obtained. In the control series, on the other hand, a significant change in K did not occur overnight before the operation. The concentration of K in the plasma of the treated patients generally rose from a subnormal level before operation to a relatively normal value during the operation, falling thereafter to the previous low level and not returning to the pretreatment level for as long as 48 hours. It seems fairly clear that this effect is directly due to the administration of desoxycorticosterone acetate. It is possible that such a depression of the concentration of K in the plasma to less then the physiologic level might have a deleterious rather than a beneficial effect, although symptoms which might be attributed to low plasma K were not observed in these patients.

In short, the changes of the constituents of the blood in the treated series do not show any essential differences as compared with those in the control series except in the case of plasma potassium and this change might as readily be considered injurious as beneficial.

Factors influencing the urinary excretion of water, chloride and sodium varied so widely as to make extremely hazardous any further conclusion based on these data.

SUMMARY

The effect of the preoperative administration of desoxycorticosterone acetate to 9 women undergoing radical mastectomy for carcinoma of the breast has been studied by means of detailed clinical observations and chemical analyses of the blood and urine. Ten additional and similar cases were studied in the same manner, but without administration of desoxycorticosterone acetate, and serve as controls.

In 6 of the control cases a fall of blood pressure to 'shock levels' accompanied by shock symptoms occurred during operation and in 2 of these 6 cases a second prolonged period of low blood pressure followed the operation. Despite ample clinical signs of shock, in no instance was elevation of the hematocrit value, total concentration of protein in the plasma or specific gravity of the plasma encountered. Instead, a decrease in these values was encountered in every instance during and after operation regardless of the condition of the patient or level of the blood pressure. Concentrations of the chemical constituents of the blood during and after the operation were remarkable chiefly for their constancy. A slight decrease in concentration of potassium in the plasma during the operation and a small but consistent decrease in concentration of chloride and sodium in the plasma after 24 hours were the most constant findings. In some cases there was a conspicuous increase of nonprotein nitrogen in the plasma after 24 hours. The changes in concentration of Na, Cl and N.P.N. in the plasma after 24 hours were in a direction which was compatible with acute adrenal cortical insufficiency and these changes therefore might be expected to prove amenable to correction by administration of desoxycorticosterone acetate.

In 6 of the patients treated with desoxycorticosterone acetate preceding the operation a fall of blood pressure to shock levels occurred during operation and in 2 of the 6 a second prolonged period of low blood pressure followed operation. The changes in the composition of the blood of the treated patients were identical with those encountered in the control series with the exception of the concentration of K in the plasma. This value usually was depressed to less than normal levels after administration of desoxycorticosterone acetate, in some instances to an extent which might be regarded as serious.

The results of this study do not provide any evidence for the hypothesis that shock as it is encountered among surgical patients is associated with acute adrenal cortical insufficiency and do not support the assumption that the preoperative administration of desoxycorticosterone acetate will prevent the appearance of surgical shock.

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ASSOCIATION NOTICE

Announcement of the Annual Meeting

THE TWENTY-SIXTH ANNUAL MEETING of The Association for the Study of Internal Secretions will be held in Atlantic City, New Jersey on Monday and Tuesday, June 8th and 9th, 1942. The Hotel Traymore will be the headquarters for registration and for the scientific and business sessions. Room reservations should be made early with the Hotel Traymore.

The Chairman of the Local Committee is Dr. Matthew Molitch, 705 Pacific Avenue, Atlantic City, New Jersey.

PRESENTATION OF PAPERS

1. The title of the paper, and a comprehensive abstract must reach the President, Dr. Edgar Allen, 333 Cedar Street, New Haven, Connecticut, not later than April 10, 1942.

Abstracts submitted should be in proper form for printing in the program. Not more than the first 200 words can be included in the printed abstract.

2. Non-members who wish to present papers must have their titles and abstracts introduced by members.

3. The abstracts of papers will be considered by the program committee and the final program announced about May 10th, 1942.

4. Papers will be limited to ten minutes for presentation. A ten-minute presentation is designed for condensed discussion of new investigations, either in laboratory or clinical phases of endocrinology. Previous publication or presentation before other societies of national membership may be cause for omitting a paper from the program.

5. Papers presented at the Annual Meeting may be submitted for publication to the Editor of ENDOCRINOLOGY or THE JOURNAL OF CLINICAL ENDOCRINOLOGY. Such submission is invited. Acceptance of a paper for the program does not necessarily mean its acceptance for publication.

You are invited to bring this announcement to the attention of your colleagues and associates who have endocrine research in progress.

NOMINATION OF OFFICERS

The By-Laws of the Association provide that nominations for all elective offices shall be made by a Nominating Committee and forwarded to the Secretary at least sixty days before the annual meeting. The Nominating Committee for the current year, appointed by the President and accepted by the Council, is as follows:

Dr. Earl T. Engle, *Chairman*, College of Physicians and Surgeons, 630 West 168th Street, New York City.
Dr. E. L. Sevringhaus, Wisconsin General Hospital, Madison, Wisconsin.
Dr. E. C. Kendall, 627 Eighth Avenue, S. W., Rochester, Minnesota.

The By-Laws also provide (Article V, Section 2) that "Any member of the Association may submit nominations to the Nominating Committee for its consideration." Nominations may be sent to the chairman, Dr. Earl T. Engle, before March 1st, 1942.

The terms of the following officers expire at the time of the annual meeting in Atlantic City in 1942.

President-Elect	E. Kost Shelton
Vice-President	E. M. K. Geiling
Secretary-Treasurer	Henry H. Turner

Council Members	*Publication Board*
David P. Barr	David P. Barr
John C. Burch	Oscar Riddle
E. C. Kendall	

THE E. R. SQUIBB & SONS AWARD

The E. R. Squibb & Sons award of $1,000.00 was established in 1939, and given first in 1940 to Dr. George W. Corner, and in 1941 to Dr. Philip E. Smith. A special committee of five members of the Association chooses an investigator or investigators in the United States or Canada for one of the best contributions to endocrinology. Nominations for the award in 1942 by members of the Association may be sent to the Secretary, Dr. Henry H. Turner, 1200 North Walker Street, Oklahoma City, Oklahoma, not later than March 1st. The nomination should be accompanied by a statement concerning the nominee's contributions to endocrinology and a bibliography of his most important publications.

Edgar Allen, *President*
Henry H. Turner, *Secretary*

Abstracts of

CURRENT CLINICAL LITERATURE

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BOOK REVIEWS

Essentials of Endocrinology. ARTHUR GROLLMAN. J. B. Lippincott Company, Philadelphia, 1941. Pp. 480.

The author sets out to select and expound the most significant and best substantiated data from the literature of endocrinology. Both laboratory and clinical data are incorporated. Such a task necessarily involves much arbitrary exclusion. In general excellent judgment has been shown in the process. The author is somewhat inclined in individual instances, however, to over-rate negative evidence as opposed to positive. Thus antihormones are dismissed as non-existent. Similarly, he sticks to his guns that the adrenal cortex produces only one hormone despite the fact that a victim of adrenal virilism may die of Addison's disease or that the urine of those harboring adrenal tumors may yield a variety of different active androgenic or estrogenic agents. However, such questionable items bulk but small in the total mass of information and the book as a whole is worthy of commendation for its succinct inclusiveness.

The subject matter is logically arranged and not difficult to read. The illustrations, which are mostly original, are well selected and satisfactorily reproduced. The format is pleasing. The book will be a welcome addition to the libraries of those who desire a not-too-technical and not-too-extensive introduction to the field of endocrinology.

Annual Review of Physiology. Ed. JAMES MURRAY LUCK. Volume 3, 1941, Annual Reviews, Inc., Stanford University, California. Pp. 784.

Increasingly scientists are coming to rely upon the Annual Review for rapid and reliable orientation toward recent developments in the broad field of physiology. The general excellence of previous volumes is maintained in this, the third. The greater space given to endocrine topics in this volume has permitted more adequate review than in the past.

Among the chapters of special interest to endocrinologists is that of E. C. Palmer and A. Ciocco on Growth. The topic is treated from an anthropological point of view but includes the outstanding publications on both human and animal subjects. The over-all rather than meticulously detailed significance of the work reviewed is presented.

E. H. Sheehan's section on the autonomic nervous system includes discussion of the secretory innervation of the chief endocrine organs as well as the pharmacology of adrenin.

S. Soskin's thoughtful chapter on metabolic functioning of the endocrine glands throws into striking relief the multifarious confusion which, at this transition period, characterizes the field.

O. Riddle discusses succinctly and informatively recent work on endocrine aspects of the physiology of reproduction. This field, too, is shown to afford relatively few consistent and adequately inclusive generalizations.

M. H. Friedman's chapter on reproduction in mammals is notable for the emphasis upon the necessity for more sophisticated control of environmental variables and for the philosophical search for rationale in explaining both concordances and discordances in existing evidence.

The Art and Science of Nutrition. ESTELLE H. HAWLEY and GRACE CARDEN. The C. V. Mosby Company, St. Louis, 1941. Pp. 619.

Nutrition is no longer a mere matter of meal planning, based upon the meager knowledge or ability of the housewife. Recognition of the role which nutrition plays in clinical medicine has become increasingly apparent and it is with the realization of the need for scientific knowledge of food and its uses, and of disease and its metabolic consequences, that the authors have outlined in this text the principles of normal nutrition and have indicated when, why, and how modifications of the normal diet may be necessary.

While the book has been written chiefly for those interested in the theory and application of nutrition it contains important information for the general practitioner and the specialist.

In chapter VI "The Endocrines and Their Role in Nutrition" the authors state "while at first thought a discussion of the endocrines, those organs which secrete powerful regulating substances into the blood, is outside the realm of nutrition, their hormones are important factors influencing the structural and nutritional conditions of the body and should be mentioned briefly." In addition to this chapter on the endocrines there are other chapters of special interest to the endocrinologist: "Nutritional Needs in Pregnancy"; "Complications in Pregnancy"; "Lactation"; "Diabetes Mellitus"; "Hypoglycemia or Hyperinsulinism"; and "Addison's Disease."

The book is attractively written and presented, with

carefully prepared diet prescriptions for normal and therapeutic needs. Many illustrations depict the more interesting and important phases of the subject matter and support the material presented in a clearly defined manner.

Simplified Diabetic Manual. ABRAHAM RUDY, M. Barrows & Company, Inc. 2nd Ed. New York. 1940. Pp. 216.

The second edition of this book carries out the same purpose as the original, bringing the subject up to date, and giving special attention to the problems arising from the use of new types of insulin.

The role of heredity and other factors in the development of diabetes are discussed and the prevention and treatment of various complications are taken up in the light of their importance.

The importance of diet in the treatment of diabetes is emphasized and 163 recipes for American, Jewish, French, German, Italian and Armenian dishes are given, so that normal food habits may be followed whenever possible.

Natural Resistance and Clinical Medicine. DAVID PERLA and JESSIE MARMORSTON. Little, Brown and Company, Boston, 1941. Pp. 1344.

In this work the authors have analyzed the various factors that determine or modify natural resistance and susceptibility, in relation to their importance in general physiology. The earlier knowledge of natural resistance or natural immunity was included under the old term "constitution" and dates back to antiquity. Modern knowledge of acquired immunity owes its origin to bacteriology and it was not until acquired immunity could be clearly separated from natural resistance and until endocrinology could demonstrate the hormonal basis for many of the manifestations of constitution that an adequate basis could be provided for the scientific investigation of natural resistance.

The remarkable progress of endocrinology over the past three or four decades has provided a sound hormonal background for the older anatomical, physiological and pathological manifestations of constitution.

Sections III and IV of the book are of special importance to the endocrinologist. Section III deals with the major topic of sex and resistance and Section IV takes up the role of other endocrine glands in resistance.

Each Chapter is summarized and very complete bibliographies have been included at the end of each chapter.

ADRENALS

NEWBURGER, R. A.

Effect of desoxycorticosterone acetate on hypochloremia in pneumonia. *J. Lab. & Clin. Med.* 26: 1642. 1941.

Desoxycorticosterone acetate (I) in sesame oil, administered intramuscularly in doses of 10 to 20 mg. per day seemed of no benefit to 3 pneumonia patients who had serum-chloride concentrations of 95.1 m.eq. per l. or less. Ten mg. of I had no effect upon the serum-chloride level and with 15 to 20 mg. the results showed a moderate rise; however, as striking a rise took place in a patient who had received only 6 g. of NaCl daily and no I. These patients were also under treatment with sulfonamide derivatives. —*H. W. Robinson* (*Courtesy Chem. Abstracts*).

LOEB, R. F.

Problems of adrenal insufficiency. *California & West. Med.* 55: 61. 1941.

The development of hypotension (which may reach extraordinarily low levels in the crises) is in part to be attributed to the disturbance of salt and water metabolism. The second physiological disorder in adrenal insufficiency is abnormal carbohydrate metabolism (hypoglycemia). Adrenal cortical extract might act as "anti-insulin." Adrenelectomized animals show a lessened work capacity. There also may be a disturbed vasomotor system. There are now more than 20 steroids isolated from the adrenal glands in crystalline form. There are 3 therapeutic agents now available in the treatment: Na salts, desoxycorticosterone acetate, adrenal cortical extracts. DCA has no demonstrable effect on carbohydrate metabolism and its effect on pigmentation is doubtful. Cortical extract has but little to recommend in correction of salt and water disturbances but might help carbohydrate metabolism slightly. Ultimate solution of the "exhaustion states" must be left to the future.—*M. L. Ilsley* (*Courtesy Biol. Abstracts*).

RHIND, E. G. G., AND A. WILSON.

Diabetes mellitus in Addison's disease. *Lancet* 37: 39. 1941.

A case of Addison's disease is described in the course of which diabetes mellitus developed. Autopsy revealed atrophy of the suprarenal glands and of the islets of Langerhans. The pathological changes suggest that there is no relationship between the number of basophil cells in the anterior lobe of the pituitary and the blood-sugar level.—*Courtesy Clin. Abstracts.*

THELANDER, H. E., AND M. CHOLFFIN.

Neonatal cortical insufficiency (Addison's disease) associated with the adrenogenital syndrome. *J. Pediat.* 18: 779. 1941.

Symptoms are divided into those produced by adrenal cortical insufficiency and by excess androgen production. The former parallel those of Addison's disease in adults, including anorexia, vomiting, diarrhea, weakness, anuria, rapid pulse, cyanosis, and extreme dehydration. Pigmentation changes are occasionally described. Death may occur in convulsions, in collapse with low temperature, extreme weakness, and coma, or in marasmus. The second group of symptoms is due to hypersecretion of androgen, which in the female produces masculinization and pseudohermaphroditism. Effects in the male are not so obvious at birth. After the first months, however, the penis is noticeably enlarged, pubic hair appears, the voice deepens and advancement in bone age occurs. The testes may not enlarge. Only one case has been studied pathologically, in which the adrenals showed bilateral, marked cortical

hypertrophy. The acute case should receive salt subcutaneously, intravenously, or both, and glucose solution may be given intravenously with normal saline. Percortin (DCA) should be administered hypodermically. After chemical balance has been established, treatment should be regulated to meet the individual need. When DCA is given, salt should be moderately restricted. A normal amount of dietary K is indicated. The advisability of surgical approach is doubtful. Ultimate prognosis of cases carried from infancy on hormones or DCA is not known. —*Courtesy Clin. Abstracts.*

ENDOCRINE GENERAL

STRASSMANN, E. O.

Endocrine treatment of masculine hairgrowth in women. *J. Internat. Coll. Surgeons* 4: 137. 1941.

Endocrine therapy in a patient with amenorrhea and polyglandular disturbance of the andropituitary type unexpectedly caused the disappearance of heavy masculine hairgrowth on the face, trunk and extremities. Nine additional cases of hirsutism combined with menstrual disorders were treated. Seven of these showed similar reactions lasting as long as the substituted hormones were effective. The dosage and timing of hormones in this treatment followed the natural cycle as closely as possible. Estrogens and gonadotropins were limited to the first and second postmenstrual weeks. During the third week only progesterone was given. One course of this type demonstrates whether the hirsuties are influenced or not; long drawn out treatments without results can thus be avoided. Since most patients with hirsuties have some type of menstrual disorder, improvement of these complaints can be expected. The use of additional thyroid tablets is beneficial in instances of low basal metabolic rate. It is pointed out that endocrine therapy for masculine hairgrowth in women is in its earliest infancy and that, for the time being, results are unpredictable and only temporary.—*Courtesy Clin. Abstracts.*

HYPOPHYSIS

PAYNE, F. L.

Hormone studies in the presence of hydatidiform mole and chorionepithelioma. *Surg., Gynec. & Obst.* 73: 86. 1941.

Eight moles and 5 chorionepitheliomas are reported with regularly spaced hormonal titrations for identification and prognostication. Demonstration of increments in values over a short period of observation are the most valuable criteria used by the author, with microscopic study of curetted tissues and finally the clinical picture in decreasing order of importance. Four types of molar activity are described: first, the actively growing tumor with marked prolan concentrations; regression with normal or slightly elevated prolan excretion; thirdly, an encapsulated or degenerating mole with decreasing prolan titre and, lastly, the missed molar abortion with less prolan concentration than that of normal pregnancy.—*R. A. Lyon (Courtesy Biol. Abstracts).*

SINGER, E.

The hormonal antigens of the anterior pituitary gland. *Australian J. Exper. Biol. & M. Sc.* 19: 125. 1941.

The antigenic properties of hormonal fractions isolated from pituitary glands were compared with analogous fractions from ox kidney. The same antigens were found in both. Observations are presented on antigens other than those associated with the known hormonal fractions, and on the influence of carbohydrate and lipoid components on the antigenicity of the pituitary gland.—*E. Eagle (Courtesy Chem. Abstracts).*

WESTMAN, A.

Urinary prolan in hyperemesis gravidarum. *Acta obst. gynec. Scandinav.* 20: 203. 1940.

Increased prolan levels were found in the urines of most of 28 patients, but no correlation between the increase and the severity of the condition was observed.—*M.M.R. (Courtesy Chem. Abstracts).*

WOODWARD, F. R., AND R. J. MAIN.

Gonadotropin excretion during the menstrual cycle. *Virginia M. Monthly* 68: 530. 1941.

The urinary gonadotropin of a woman 25 years old who was taking thyroid regularly, was determined over two 30-day periods. The amount of hormone excreted was marked and irregular. Similar results were obtained when using the first morning or the 24 hour specimen of urine. No correlation of gonadotropin excretion with intercourse was found.—*R. J. Main (Courtesy Biol. Abstracts).*

PANCREAS

MAGNER, W.

Hyperinsulinism: a report of 2 cases. *Canad. M. A. J.* 45: 49. 1941.

Two cases of hyperinsulinism are reported. In the first case operation revealed a single islet adenoma which was removed with great ease. In the second case no tumor nodule was found; the body and tail of the pancreas were excised. Following the operation both patients were completely relieved of hypoglycemic symptoms.—*Courtesy Clin. Abstracts.*

MELLINGHOFF, K., AND G. VOGES.

Action of depot insulin in normal subjects. *Deutsches Arch. f. klin. Med.* 185: 345. 1939.

Forty U of various depot insulins and of insulin were injected into normal subjects maintained on a standard diet. Hypoglycemia occurs as rapidly with depot insulin as with ordinary insulin.—*B.C.P.A.*

THYROID

ABRAMSON, D. I., AND S. M. FIERST.

The peripheral vascular response to exercise in the hyperthyroid state. *J. Clin. Investigation* 20: 517. 1941.

The rate of blood flow in the forearm was determined

by means of the venous occlusion plethysmographic method. The blood flow repayment following exercise was much greater in the hyperthyroid state than in the period following subtotal thyroidectomy. A correlation was apparent between the level of O_2 consumption and the magnitude of the excess blood flow elicited by the exercise. Exercise placed a much greater load upon the circulation in hyperthyroidism than in the normal state.—*D. I. Abramson.*

BAINBRIDGE, W. S.

The toxemias and the thyroid gland. *J. Internat. Coll. Surgeons* 4: 233. 1941.

Illustrative cases are cited in which the relief of somatic factors, with or without operation on the gland itself, cured some pathologic conditions of the thyroid. It is concluded that certain conditions of the thyroid gland are due to foci of infection at distant points. Toxic irritation in the blood affects the cells; thus the activity of the gland may either be augmented or diminished, or the character of its secretion changed. One of the many causes of thyroid pathology is chronic intestinal toxemia. A goiter whose size diminishes and whose accompanying symptoms disappear after surgical or therapeutic measures on the intestinal tract (or other suspected source of infection) is undoubtedly caused by the absorption of that particular toxin.—*Courtesy Clin. Abstracts.*

BASSETT, A. M., A. H. COONS AND W. T. SALTER.

Protein-bound iodine in blood. V. Naturally occurring iodine fractions and their chemical behavior. *Am. J. M. Sc.* 202: 516. 1941.

The protein-bound I in blood plasma of man and of animals resides chiefly in the traditional albumin fraction. This I is subject to fluctuations dependent upon thyroid activity. Such fluctuations, in absolute terms, are due chiefly to a thyroxine-like moiety. The moiety resembling diiodotyrosine might increase proportionately, but it contributes relatively little to the absolute change from the normal level. Accordingly, total protein-bound I fluctuates largely with thyroxine-like I. In myxedema, the thyroxine-like fraction practically disappears. Despite variations in this protein-bound I, the ionized I (inorganic) was rather low and approximately constant regardless of the state of thyroid activity. Nevertheless, it increased markedly when extraordinary, though perhaps very small, amts. of I entered the organism. Simultaneously a false increase in the protein-bound I occurred which could be reproduced by the addition of iodide to plasma in vitro. The protein-bound thyroxine-like moiety of the plasma I is a good objective index of circulating thyroid hormone. Plasma protein-bound I might be used clinically to confirm physiologic thyroid status.—*W. T. Salter.*

BUÑO, W.

Pseudotuberculous follicules in goitres (Formaciones pseudotuberculosas en los bocios). *Arch. Soc. de biol. de Montevideo* 10: 26. 1940.

Pseudotuberculous follicules without caseosis and with no tendency toward progressive development are described. The author believes that they are formed by cells of conjunctive tissue origin, because it was observed that the connective tissue buds into vesicles, and because of the behaviour toward blood pigment.—*J. E. Mackinnon* (*Courtesy Biol. Abstracts*).

CUTLER, E. C., AND S. O. HOERR.

Total thyroidectomy for heart disease. A five-year follow-up study. *Ann. Surg.* 113: 245. 1941.

A 5-year follow-up study is presented of 57 consecutive cases of total thyroidectomy performed for heart disease during 1932, 1933 and 1934. The majority of the patients had been unrelieved by medical therapy and presented a serious operative risk. There were 12 five-year survivors in the group of 32 with angina pectoris, and 4 five-year survivors in the group of 25 who had congestive failure. There were 5 postoperative deaths; 4 of these, as well as all but 3 of the later deaths, were attributable to heart disease. The best results were obtained in patients with angina pectoris. Twenty-six of the 27 patients surviving more than 6 months were relieved of pain in some degree for six months or longer, and 8 of the 12 five-year survivors had sustained relief. Preoperative evidence of congestive failure or cardiac enlargement was an unfavorable prognostic sign for long survival. In congestive failure the 5-year results were disappointing. Fifteen of the 25 patients lived for 6 months or more, and 12 of these had relief for 6 months or longer. Of 4 five-year survivors, 3 showed sustained relief; 2 of these 3 have died of congestive failure in the sixth year after operation. Results were better in the group having congestive failure from chronic rheumatic valvular disease than from arteriosclerotic or hypertensive heart disease.—*Courtesy Clin. Abstracts.*

KING, J. D., AND F. E. HAMILTON.

The iodine content of the normal human thyroid gland and its correlated histology. *West. J. Surg.* 49: 231. 1941.

An extensive survey of pertinent literature revealed marked variation in gross appearance, histological structure and I content of the normal gland. Glands from 'goitrous' regions average 45.1 to 63.3 gm., I concentration 53 mg.% dry weight, and possess the smallest follicles, highest % of epithelial proliferation and of nodule formation. Glands from 'moderately goitrous' regions average 17 to 37.5 gm., I concentration 84 mg.% dry weight, and are medium and moderate as to epithelial proliferation, size of follicles and incidence of nodule formation. Glands from non-goitrous regions average 12.5 to 25 gm., I concentration 234 mg. % dry weight, and show the largest follicles, lowest % of epithelial proliferation and lowest incidence of nodule formation. An extensive bibliography is appended.—*H.O.H.*

LICHTMAN, S. S.

Liver function in hyperthyroidism, with special reference to the galactose tolerance test. *Ann. Int. Med.* 14: 1199. 1941.

Employing various clinical liver function tests, 45 to

90% of cases of hyperthyroidism show some functional impairment, usually of slight to moderate degree. Results of the galactose tolerance test may be most uniformly correlated with clinical criteria of severity of thyrotoxicosis, e.g., weight loss, duration of the disease, and B.M.R. Other tests show poor correlation or none. Factors which may directly improve impaired liver function are administration of I and partial or subtotal thyroidectomy. Normal function may be restored. On the other hand, upper respiratory infections and other infections may aggravate existent liver function disturbance even in absence of fever. A mechanism for the hepatic function derangement in hyperthyroidism is suggested based upon loss of a protective factor in the depletion of liver glycogen.—*H.O.H.*

McGregor, J. K.

Recurrent hyperthyroidism. *J. Internat. Coll. Surgeons* 4: 239. 1941.

Theoretically, nodular toxic goiters should not recur following operation, provided that practically total thyroidectomies were done. Nevertheless, at least 25% of the author's cases of diffuse toxic hyperthyroidism have shown some signs of recurrence. The greater the urge from without the thyroid, the more chance there is of a recurrence; in other words, polyglandular types recur in spite of complete operation. The author believes that recurrent hyperthyroidism is regional, as is the severity of the disease. Recurrences are treated by iodine, which may be necessary for the remainder of the patient's life. Secondary operations should be left until all other methods have been tried. Radiation of the thyroid gland is always used as a preliminary measure, and radiation of the suprarenals and pituitary has been recently used with satisfactory results. —*Courtesy Clin. Abstracts.*

Riggs, D. S., E. F. Gildea and E. B. Man.

The clinical interpretation of blood iodine levels. *Connecticut M. J.* 5: 209. 1941.

In clinical hyperthyroidism the blood I was elevated; in most instances the level was 2 to 6 times the highest normal quantity. Patients with spontaneous myxedema or with postoperative hypothyroidism had blood I values well below the normal range.—R. *Berggren* (*Courtesy Chem. Abstracts*).

Riggs, D. S., E. F. Gildea, E. B. Man and J. P. Peters.

Blood iodine in patients with thyroid disease. *J. Clin. Investigation* 20: 345. 1941.

A reinvestigation of blood I in patients with thyroid disorders has been undertaken because it has been found that many of the older methods yielded erroneously high normal values. The blood I levels have been determined in 55 patients with a number of different symptoms and signs of thyroid disorder. The results have been analyzed in an attempt to determine the relation of blood I to the symptoms and signs of hyperthyroidism. The level of blood I has been found to be closely related to thyroid activity. In 31 patients with hyperthyroidism the blood I ranged between 6.4 and 21.9γ%. In 7 patients with myxedema it varied from 0.3 to 1.7γ%. There was no overlapping with the normal range of 2.4 to 4.2γ% in 26 euthyroid subjects. Six patients with nodular goiters but without symptoms of thyroid overactivity had blood I which did not differ significantly from normal. Elevated blood I values are invariably found in hyperthyroid patients. However, certain patients without manifest hyperthyroidism may also have an elevated blood I.—*Courtesy Clin. Abstracts.*

Salter, W. T., A. M. Bassett and T. S. Sappington.

Protein-bound iodine in blood. VI. Its relation to thyroid function in 100 clinical cases. *Am. J. M. Sc.* 202: 527. 1941.

A series of 100 cases of suspected thyroid disturbance and 10 control individuals has been analyzed from the standpoint of final clinical diagnosis, B.M.R. and plasma protein-bound I. When the first 2 of these criteria are in agreement, there is a close correlation between the plasma I and the B.M.R. Such cases amount to 71% of the entire group studied. Of the remaining 29%, the B.M.R. often did not clearly reflect the clinical status and the plasma protein-bound I proved much more reliable. This was particularly true in the group of "Graves' disease without hyperthyroidism" in which the B.M.R. ranged from −20 to +40%, but the plasma protein-bound I was normal. These data constitute additional evidence for the possible dissociation of physiologic hyperthyroidism and clinical Graves' disease. In hypothyroidism, plasma protein-bound I is a highly reliable criterion for confirming lack of thyroid hormone, even when full-blown myxedema is absent. The simplified chemical procedures employed are partly empirical. Their use is justified by their consistency with clinical data, but due care should be exercised in comparing the data with the results obtained by other methods.—*W. T. Salter.*

Sherrill, J. W., and E. M. Mackay.

Hypothyroidism and bladder function; an experimental study. *J. Urol.* 46: 34. 1941.

Atony of the bladder observed in patients suffering from hypothyroidism stimulated an experimental study of the relation of these conditions in the albino rat. Hypothyroid rats regularly showed bladder atony as measured by the filled area shown by a radio-opaque compound in urine-bladder emptying time and the lowered ability to sustain an artificial increase in the intra-bladder pressure. —*Authors' summary.*